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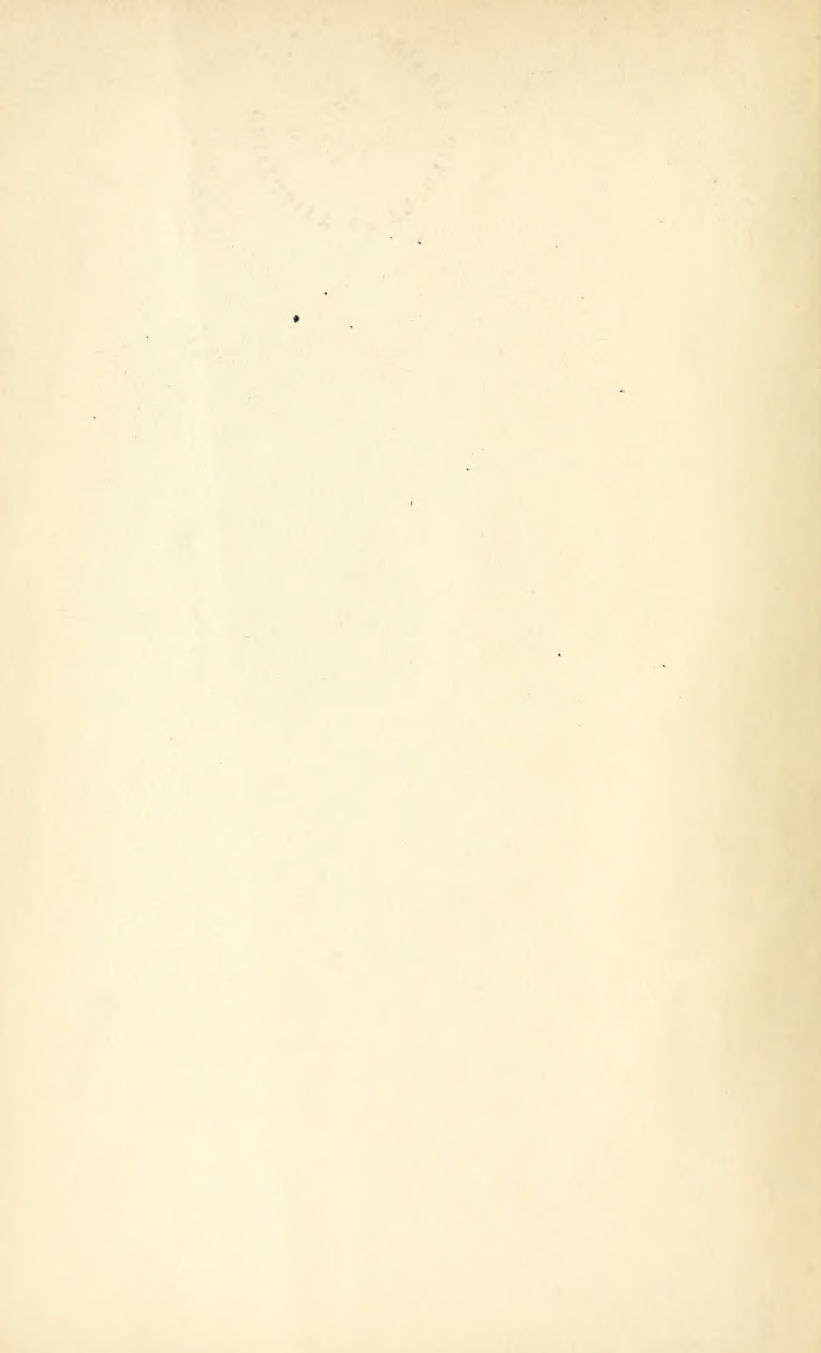
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## CONTENTS OF VOLUME XV

### JANUARY, 1915. NUMBER 1

	PAGE
THE VENTILATORY FUNCTION OF THE LUNG IN EMPHYSEMA AND ASTHMA. C. F. HOOVER, M.D., AND LESTER TAYLOR, M.D., CLEVELAND.....	1
EFFECT OF INTRAVENOUS AND INTRASPINAL TREATMENTS ON CEREBROSPINAL SYPHILIS. GEORGE DRAPER, M.D., NEW YORK.....	16
THE MECHANISM OF LABYRINTHINE NYSTAGMUS AND ITS MODIFICATIONS BY LESIONS IN THE CEREBELLUM AND CEREBRUM. J. GORDON WILSON, M.D., CHICAGO, AND F. H. PIKE, PH.D., NEW YORK.....	31
THE RELATION OF PANCREATIC ORGANO-THERAPY TO KETOGENESIS. EDWIN GARVEY KIRK, M.D., CHICAGO.....	39
STUDIES ON THE PATHOLOGICAL PHYSIOLOGY OF THE HEART. I. THE INTRA-AURICULAR, INTRAVENTRICULAR AND AORTIC PRESSURE CURVES IN AURICULAR FIBRILLATIONS. CARL J. WIGGERS, M.D., NEW YORK.....	77
THE DISTRIBUTION OF IODIN IN THE CELL FOLLOWING ADMINISTRATION OF ORGANIC IODIN PREPARATIONS. FRANKLIN C. McLEAN, M.S., M.D., PORTLAND, ORE. ....	92
STATISTICS OF PELLAGRA IN SPARTANBURG COUNTY, S. C., INCLUDING GEOGRAPHICAL DISTRIBUTION OF THE DISEASE AND ITS RELATION TO RACE, AGE, SEX AND OCCUPATION. J. F. SILER, M.D., P. E. GARRISON, M.D., AND W. J. MACNEAL, M.D., NEW YORK.....	98
MENTAL AND NERVOUS DISORDERS ASSOCIATED WITH PELLAGRA. H. DOUGLAS SINGER, M.D., M.R.C.P., KANKAKEE, ILL.....	121
FURTHER OBSERVATIONS ON THE BLOOD-COUNT IN PELLAGRA. OLIVER S. HILLMAN, M.D., AND PAUL A. SCHULE, M.D., NEW YORK.....	147
STREPTOCOCCUS VIRIDANS IN ITS RELATION TO INFECTIONS OF THE UPPER RESPIRATORY TRACT. RUSSELL L. CECIL, M.D., NEW YORK.....	150
A CASE OF INDEPENDENT VENTRICULAR ACTIVITY OCCURRING DURING ACUTE ARTICULAR RHEUMATISM. SELIAN NEUHOF, M.D., NEW YORK.....	169
BOOK REVIEWS:	
DISEASES AND ITS CAUSES. BY W. T. COUNCILMAN.....	177
BLOOD-PRESSURE: ITS CLINICAL APPLICATIONS. BY GEORGE WILLIAM NORRIS, A.B., M.D. ....	177
THE MENTAL HEALTH OF THE SCHOOL CHILD. BY J. E. WALLACE WALLIN, PH.D. ....	177
PROBLEMS OF GENETICS. BY WILLIAM BATESON, M.A., F.R.S.....	178
A TEXT-BOOK OF MEDICAL DIAGNOSIS. BY JAMES M. ANDERS, M.D., PH.D., LL.D., AND L. NAPOLEON BOSTON, A.M., M.D.....	178

### FEBRUARY, 1915. NUMBER 2

	PAGE
ACTION OF ATOPHAN AND NOVATOPHAN IN GOUT AND IRITIS. C. A. SMITH, M.S., AND P. B. HAWK, PH.D., PHILADELPHIA.....	181
THE RADIO-ACTIVITY OF THE MINERAL WATERS OF HOT SPRINGS, WARM SPRINGS AND HEALING SPRINGS IN HOT SPRINGS, VA. JOHN C. HEM-METER, M.D., AND ERNEST ZUERLIN, M.D., BALTIMORE.....	188
A STUDY OF DIFFERENT NITROGENOUS DIETS IN CHRONIC NEPHRITIS. CHAN-NING FROTHINGHAM, JR., M.D., AND WILSON G. SMILLIE, M.D., BOSTON	204
METABOLISM STUDY OF A CASE OF CONGENITAL HEMOLYTIC JAUNDICE WITH SPLENOMEGALY. JAMES P. McKELVY, M.D., AND JACOB ROSENBLUM, M.D., PH.D., PITTSBURGH .....	227
FUNCTIONAL CHANGES IN EXPERIMENTAL HYDRONEPHROSIS. N. M. KEITH, M.D., AND R. R. SNOWDEN, M.D., BALTIMORE.....	239

# CONTENTS OF VOLUME XV

## FEBRUARY—Continued

	PAGE
FURTHER OBSERVATIONS ON THE EMPLOYMENT OF SPECIFIC AND NON-SPECIFIC ANTIGENS IN THE PERFORMANCE OF THE GONOCOCCIC COMPLEMENT-FIXATION TEST. B. A. THOMAS, M.D., R. H. IVY, M.D., AND J. C. BIRD-SALL, M.D., PHILADELPHIA .....	265
HOW SHALL WE TELL WHETHER OR NOT THE MYOCARDIUM IS COMPETENT? JOHN M. SWAN, M.D., ROCHESTER, N. Y.....	269
THE THERAPEUTIC ACTION OF IODIN. JAMES W. JOBLING, M.D., AND WILLIAM PETERSEN, M.D., NEW YORK.....	286
OBSERVATIONS ON RENAL FUNCTION IN ACUTE EXPERIMENTAL UNILATERAL NEPHRITIS. W. C. QUINBY, M.D., AND R. FITZ, M.D., BOSTON.....	303
STUDIES IN PAROXYSMAL EDEMA. WALTER W. PALMER, M.D., BOSTON.....	329
BOOK REVIEWS:	
L'ALTERNANCE DU COEUR: ETUDE CRITIQUE. PAR LAURENT GRAVIER...	339
THE LIFE AND LETTERS OF NATHAN SMITH, M.B., M.D. BY EMILY A. SMITH. WITH AN INTRODUCTION BY WILLIAM H. WELCH, M.D., LL.D. ....	340

## MARCH, 1915. NUMBER 3

	PAGE
MALIGNANT SYMPATHICUS TUMOR OF THE RIGHT SUPRARENAL. DANIEL J. GLOMSET, M.D., DES MOINES, IOWA.....	341
UREMIA. III. THE NON-PROTEIN NITROGEN OF BLOOD. NELLIS B. FOSTER, M.D., NEW YORK .....	356
THE EFFECT OF ANESTHESIA AND OPERATION ON THE KIDNEY FUNCTION, AS SHOWN BY THE PHENOLSULPHONEPHTHALEIN TEST. RICHARD H. MILLER, M.D., IN COLLABORATION WITH HUGH CABOT, M.D., BOSTON.....	369
INTESTINAL OBSTRUCTION. AN EXPERIMENTAL STUDY OF THE CAUSES OF SYMPTOMS AND DEATH. FRED T. MURPHY, M.D., AND BARNEY BROOKS, M.D., ST. LOUIS .....	392
A WORKING HYPOTHESIS OF HEMOGLOBIN PIGMENT METABOLISM. T. ADDIS, M.D., SAN FRANCISCO .....	413
A REPORT OF THE BACTERIOLOGICAL EXAMINATION OF ENLARGED LYMPH-NODES REMOVED FROM A PATIENT WITH HODGKIN'S DISEASE. LAWRENCE J. RHEA, M.D., AND E. H. FALCONER, M.D., MONTREAL, CAN.....	438
THE OCCURRENCE OF MALIGNANT NEOPLASMS IN THE YOUNG AS SHOWN BY AN ANALYSIS OF 2,000 CASES OF MALIGNANT NEOPLASMS EXAMINED IN THE PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN. ALDRED SCOTT WARTHIN, M.D., ANN ARBOR, MICH.....	444
EXPERIMENTAL DIABETES INSIPIDUS IN DOGS. S. A. MATTHEWS, LAWRENCE, KAN. ....	451
THE USE OF STRYCHNIN AND CAFFEIN AS CARDIOVASCULAR STIMULANTS IN THE ACUTE INFECTIOUS DISEASES. L. H. NEWBURGH, M.D., BOSTON .....	458
IMMUNITY TESTS IN COCCIDIOIDAL GRANULOMA. JEAN V. COOKE, M.D., SAN FRANCISCO .....	479
THE VALUE OF THE ELECTROCARDIOGRAM IN THE DIAGNOSIS OF CARDIAC HYPERTROPHY. E. W. BRIDGMAN, M.D., BALTIMORE.....	487

## APRIL, 1915 NUMBER 4

	PAGE
THE DEAD SPACE IN MODERATE AND LARGE RESPIRATORY VENTILATION. C. F. HOOVER, M.D., AND JULIAN E. GAMMON, M.D., CLEVELAND.....	501
THE OCCURRENCE OF NUCLEAR PARTICLES IN THE ERYTHROCYTES FOLLOWING SPLENECTOMY. ROGER S. MORRIS, M.D., CLIFTON SPRINGS, N. Y.....	514
AGE INCIDENCE IN SARCOMA. CARL VERNON WELLER, M.D., ANN ARBOR, MICH. ....	518
STUDY XXIII. THE RELATION BETWEEN AMYLASE RETENTION AND EXCRETION AND NON-PROTEIN NITROGEN RETENTION IN EXPERIMENTAL URANIUM NEPHRITIS. R. FITZ, M.D., BOSTON.....	524
FURTHER STUDIES OF RENAL FUNCTION IN RENAL, CARDIORENAL AND CARDIAC DISEASES. L. G. ROWNTREE, M.D., E. K. MARSHALL, JR., PH.D., AND W. A. BAETJER, M.D., BALTIMORE.....	543



# CONTENTS OF VOLUME XV

## APRIL—Continued

	PAGE
THE EFFECTS OF SODIUM SALICYLATE ON VARIOUS TYPES OF EXPERIMENTAL ARTHRITIS. DAVID JOHN DAVIS, M.D., CHICAGO.....	555
SKIAGRAPHIC STUDY OF THORAX, THORACIC WALL AND THORACIC VISCERA. L. B. BIBB, M.D., AND C. E. GILLILAND, M.D., AUSTIN, TEXAS.....	558
METASTATIC CALCIFICATION. H. GIDEON WELLS, CHICAGO.....	574
STUDIES IN PANCREATIC DISEASE. BURRILL B. CROHN, M.D., NEW YORK....	581
A DIFFERENTIAL STUDY OF COCCIDIOIDAL GRANULOMA AND BLASTOMYCOSIS. I. PATHOLOGY AND BACTERIOLOGY. II. REPORT OF TWO ADDITIONAL CASES OF COCCIDIOIDAL DISEASE. PHILIP KING BROWN, M.D., AND W. TAYLOR CUMMINS, M.D., SAN FRANCISCO.....	608
THE SPECIFIC GRAVITY OF THE HUMAN BODY. C. D. SPIVAK, M.D., DENVER	628
BOOK REVIEW: CHEMICAL PATHOLOGY. BY H. GIDEON WELLS, PH.D., M.D.	643

## MAY, 1915. NUMBER 5. PART 1

	PAGE
AN INVESTIGATION OF THE POTENCY OF TINCTURE OF ACONITE. G. CANBY ROBINSON, M.D., ST. LOUIS.....	645
NUCLEAR DIGESTION AND URIC ACID EXCRETION IN A CASE OF TOTAL OCCLUSION OF THE PANCREATIC DUCT. DANA W. ATCHLEY, BALTIMORE.....	654
SECONDARY HYPERTROPHIC OSTEO-ARTHROPATHY AND ITS RELATION TO SIMPLE CLUB-FINGERS. EDWIN A. LOCKE, M.D., BOSTON.....	659
CHRONIC ULCERATIVE COLITIS WITH POLYPS. A CONSIDERATION OF THE SO-CALLED COLITIS POLYPOSA (VIRCHOW), J. H. HEWITT, M.D., AND W. T. HOWARD, M.D., CLEVELAND.....	714
OBSERVATIONS ON THE USE OF THE ABDERHALDEN REACTION WITH NORMAL AND PATHOLOGICAL HUMAN SERUMS. ELLISON L. ROSS, PH.D., AND H. DOUGLAS SINGER, M.D., KANKAKEE, ILL.....	724
THE FACTORS OF COAGULATION IN PRIMARY PERNICIOUS ANEMIA. CECIL K. DRINKER, M.D., AND SAMUEL H. HURWITZ, M.D., BOSTON.....	733
THE ORIGIN OF THE PROTEINS OF NEPHRITIC URINE. A. L. CAMERON, M.D., AND H. GIDEON WELLS, M.D., CHICAGO.....	746
MERCURY NEPHRITIS. N. B. FOSTER, M.D., NEW YORK.....	754
THE OCULAR REFLEX. AN ELECTROCARDIOGRAPHIC STUDY WITH SPECIAL REFERENCE TO THE DIFFERENCES BETWEEN RIGHT AND LEFT VAGAL AND OCULAR PRESSURES IN TABETICS AND NON-TABETICS. SAMUEL A. LEVINE, M.D., BOSTON .....	758
COARSE AURICULAR FIBRILLATION IN MAN. A. W. HEWLETT, M.D., AND F. N. WILSON, M.D., ANN ARBOR, MICH. ....	786

## MAY, 1915. NUMBER 5. PART 2

	PAGE
CLINICAL CALORIMETRY. FIRST PAPER. A RESPIRATION CALORIMETER FOR THE STUDY OF DISEASE. GRAHAM LUSK, NEW YORK.....	793
CLINICAL CALORIMETRY. SECOND PAPER. THE RESPIRATION CALORIMETER OF THE RUSSELL SAGE INSTITUTE OF PATHOLOGY IN BELLEVUE HOSPITAL. J. A. RICHE AND G. F. SODERSTROM, NEW YORK.....	805
CLINICAL CALORIMETRY. THIRD PAPER. THE ORGANIZATION OF A SMALL METABOLISM WARD. FRANK C. GEPHART, A.B., AND EUGENE F. DUBOIS, M.D., NEW YORK .....	829
CLINICAL CALORIMETRY. FOURTH PAPER. THE DETERMINATION OF THE BASAL METABOLISM OF NORMAL MEN AND THE EFFECT OF FOOD. FRANK C. GEPHART, A.B., AND EUGENE F. DUBOIS, M.D., NEW YORK.....	835
CLINICAL CALORIMETRY. FIFTH PAPER. THE MEASUREMENT OF THE SURFACE AREA OF MAN. DELAFIELD DUBOIS, B.S., AND EUGENE F. DUBOIS, M.D., NEW YORK.....	868
CLINICAL CALORIMETRY. SIXTH PAPER. NOTES ON THE ABSORPTION OF FAT AND PROTEIN IN TYPHOID FEVER. WARREN COLEMAN, M.D., AND FRANK C. GEPHART, A.B., NEW YORK.....	882
CLINICAL CALORIMETRY. SEVENTH PAPER. CALORIMETRIC OBSERVATIONS ON THE METABOLISM OF TYPHOID PATIENTS WITH AND WITHOUT FOOD. WARREN COLEMAN, M.D., AND EUGENE F. DUBOIS, M.D., NEW YORK..	887
CLINICAL CALORIMETRY. EIGHTH PAPER. ON THE DIABETIC RESPIRATORY QUOTIENT. GRAHAM LUSK, NEW YORK.....	939

# CONTENTS OF VOLUME XV

JUNE, 1915. NUMBER 6

	PAGE
VARIATIONS IN THE TOXICITY OF CHLOROFORM FOR ANESTHESIA. WORTH HALE, M.D., BOSTON.....	945
THE RELATION OF THE PURGATIVE ACTION OF MAGNESIUM SULPHATE TO PERISTALSIS, AND THE GENERAL LAW OF CROSSED INNERVATION. S. J. MELTZER, M.D., NEW YORK.....	955
STUDIES IN RENAL FUNCTION WITH SPECIAL REFERENCE TO NON-PROTEIN NITROGEN AND SUGAR CONCENTRATION IN THE BLOOD, PHENOLSULPHONE- PHTHALEIN ELIMINATION AND BLOOD PRESSURE. ARTHUR H. HOPKINS, M.D., AND LEON JONAS, M.D., PHILADELPHIA.....	964
A STUDY OF GENERAL AND LOCALIZED EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN IN CASES OF HUMAN CANCER. C. B. MCCLURG, M.D., W. O. SWEET, M.D., H. N. LYON, M.D., M. S. FLEISHER, M.D., AND LEO LOEB, M.D., ST. LOUIS.....	974
RAT-BITE FEVER. BURRILL B. CROHN, M.D., NEW YORK.....	1014
FACTORS INVOLVED IN SOME CASES OF PLEURAL FLUID ASSOCIATED WITH NORMAL OR INCREASED VOCAL RESONANCE. CHARLES M. MONTGOMERY, M.D., AND ENGELHARDT A. ECKHARDT, PH.D., PHILADELPHIA.....	1040
THE RELATION OF URIC ACID TO GOUTY ATTACKS. AMY L. DANIELS, PH.D., MADISON, WIS., AND FRANCIS H. MCCRUDDEN, M.D., BOSTON..	1046
STUDY XXIV; THE EFFECT OF THEOBROMIN SODIUM SALICYLATE IN ACUTE CHROMATE NEPHRITIS. JAMES P. O'HARE, M.D., BOSTON.....	1053
CERTAIN ASPECTS OF BIOLOGICAL OXIDATION. A. S. LOEVENHART, M.D., MADISON, WIS. ....	1059
UROBILIN IN THE STOOL—AN INDEX TO BLOOD DESTRUCTION. OSWALD H. ROBERTSON, M.D., BOSTON.....	1072
THE EFFECT OF REPEATED INJECTIONS OF FOREIGN PROTEIN ON THE HEART MUSCLE. W. T. LONGCOPE, M.D., NEW YORK.....	1079
INDEX .....	1085

# The Archives of Internal Medicine

Vol. XV

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No. 1

## THE VENTILATORY FUNCTION OF THE LUNG IN EMPHYSEMA AND ASTHMA\*

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CLEVELAND

This study of emphysema and asthma was undertaken with the idea that great changes in the dead space must occur when an emphysematous patient suffered an asthmatic attack.

It was suggested in a former publication on emphysema<sup>1</sup> that the dead space was probably much enlarged in emphysema. If this were true then the dead space of an emphysematous patient must undergo a great change during an attack of asthma. We have succeeded in getting two emphysematous patients who had frequent attacks of asthma. After some persuasion, these patients learned to breathe through the Zuntz apparatus during asthmatic attacks. The asthma of both patients could always be relieved by subcutaneous injections of epinephrin. In this way we had numerous opportunities to compare the minute volume of air and the alveolar air of the emphysematous state with the asthmatic state. Much to our surprise we found the dead space, as measured by our method, varied little in the two conditions. Furthermore, we found the minute volume remained nearly the same, the concentration of carbon dioxid in the alveolar air was increased very little during the asthmatic attacks, but in spite of these slight variations in lung ventilation the patients commonly were cyanotic during the attacks of asthma and we could not account for cyanosis by any changes in the circulatory system.

To produce cyanosis by impairment in the circulation, the evidences of stasis must be very great. Sufficient stasis may occur to cause air hunger, marked cardiac enlargement and pronounced stasis in the venous system as evidenced by widening of the jugular veins and hepatic enlargement, and, in spite of all these signs, cyanosis may not be apparent.

The problem then presents itself in this wise. An emphysematous patient may have an attack of asthma which will modify the measur-

\* Submitted for publication, July 23, 1914.

1. Hoover, C. F.: The Minute Volume and Alveolar Air in Pulmonary Emphysema, *THE ARCHIVES INT. MED.*, 1913, xi, 52.



able lung ventilation very little and not cause any demonstrable changes in the circulation, but cyanosis commonly occurs. What may then account for the cyanosis? Some alteration in the function of external respiration owing to changes in the respiratory membrane during asthma? Or is there some factor in lung ventilation which we have thus far failed to take into account?

From our observations we have come to the conclusion that certainly a factor thus far unrecognized in lung ventilation is one cause, and, possibly, changes in the respiratory membrane during asthma may be another cause of cyanosis in asthma.

As was stated, when we began our observations we sought to compare the dead space of asthma with the dead space of emphysema, but our results failed to show any essential change in the size of the dead space. Sometimes the results showed a larger dead space in asthma and at other times the results were reversed. At no time was the change in the dead space sufficiently large to have any significance. Our method was to collect specimens of the expired air and measure the minute volume of air, and also procure specimens of alveolar air during the asthmatic attacks, then we repeated these procedures directly after the asthma was relieved. It is obvious that the entire carbon dioxid is contained in the alveolar air and the air of the dead space will contain no carbon dioxid. At least this is true for an instant at the end of an inspiratory effort. With expiration the alveolar air and dead-space air are expelled together, but the air at the end of the expiration will be free of dead space air, so by knowing the carbon dioxid content of the total expired air and the carbon dioxid percentage in the alveolar air we can easily estimate the total amount of alveolar air. Therefore, the dead space will equal the total expired air minus the alveolar air. If, for instance, a total expiration equals 1,000 c.c. and its carbon dioxid content equals 5 per cent. and the carbon dioxid content of the alveolar air equals 5.5 per cent., then the total alveolar air equals

$$\frac{0.05 \times 1,000}{0.055} = 909 \text{ c.c.}$$

therefore the dead space is  $1,000 - 909 = 91 \text{ c.c.}$

It is clear, then, that the dead space estimated in this manner will depend on the volume of expired air and the disparity between the carbon dioxid content of the expired air and the carbon dioxid content of the alveolar air. In our observations on asthmatic patients we employed the Zuntz method, which is not sufficiently accurate for estimating the dead space, but it is accurate enough for comparative studies of the ventilatory function of the lung.

The minute volume specimens of air collected with the Zuntz apparatus are supposed to be collections composed of very minute

parts of each expiration. If a specimen of 50 c.c. is collected from a patient breathing fifteen times a minute for ten minutes and each expiration equals 800 c.c., then it must be assumed that from each expiration of 800 c.c., 0.33 c.c. of air enters the collecting tube. Therefore, to be a perfect sample of the expired air, this 0.3 c.c. of air must be composed of the same proportions of air from the dead space and the alveolar air which are represented in the total expiration of 800 c.c. This cannot be expected, because the air of an entire expiration is not delivered with the same pressure throughout the entire expiratory phase, and if the pressure of expiration plays any part in the displacement of the liquid in the sampling-tube there will be more displacement in the first part of an expiration than in the latter part. The turning of the spindle of the spirometer is therefore not the only factor which may cause replacement of the contained fluid with air. Were the revolving spindle the only factor to replace the fluid with air in the sampling-tube there is another source of error, whether mercury or acidulated water is used in the tube. The discharge of the fluid is in drops and not in a graduated stream of minute proportions as should occur if the sample of air is to be a collection of the total expired air in miniature, consequently air replaces each drop as it escapes from the tube, and it is a mere chance at just what part of expiration this replacement of liquid by air takes place. The results are fairly constant, but when a sample of air obtained with the Zuntz apparatus is compared with the total expired air collected in a rubber bag it is found the Zuntz specimens have a lower carbon dioxid content. We take this to be evidence that a disproportionately large part of the first portion of each expiration is captured in the sampling-tube, as this portion of an expiration is delivered under higher pressure than is the latter portion of an expiration; and the first part of an expiration has a lower carbon dioxid content than the latter part. For this reason the dead space is reckoned larger when the Zuntz apparatus is used than when the entire expiration is captured and compared with the alveolar air. When the Zuntz apparatus was used, Patient R. J. gave the following result:

Minute volume equals .....	9,000 c.c.
Respiratory rate equals .....	21 per minute
Each respiration equals .....	428 c.c.
Carbon dioxid in alveolar air equals..	5.2 per cent.
Carbon dioxid in expired air equals...	1.9 per cent.

When the rubber bag was employed to collect the minute volume or total expired air:

Minute volume equals .....	9,000 c.c.
Respiratory rate equals .....	24 per minute
Each respiration equals .....	425 c.c.
Carbon dioxid in alveolar air equals..	5.0 per cent.
Carbon dioxid in expired air equals...	3.58 per cent.

From many estimates made by the two methods during different periods of our studies it is quite clear that specimens of the total expired air collected by the Zuntz apparatus give too low a percentage of carbon dioxide.

The first question to be settled is whether stenosis of any and all parts of the air-passages will cause an increased volume of the affected lung area.

That the lung increases in volume during bronchiolar spasm is perfectly clear, but bronchiolar spasm may carry with it some other factor than mere stenosis of the air-passages.

During the past year, one of us saw a child with laryngeal diphtheria which caused marked stenosis of the larynx, but the stenosis was not severe enough to cause cyanosis. There was descent of the lower lung borders and also descent of the entire diaphragm, as was clearly proved by strong inspiratory narrowing of the subcostal angle.

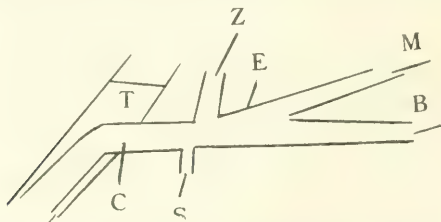


Diagram of cannula by which samples of air were taken for analysis. *T*, trachea; *C*, cannula; *Z*, branch to Zuntz apparatus; *S*, lateral opening for sampling air; *M*, branch of mercury manometer; *B*, branch to bottle of 2,540 c.c. capacity; *E*, clamp.

We also employed some animal experiments to prove the same point. Dogs were first anesthetized with ether and then (after tracheotomy) a cannula was securely fixed in the trachea. The dogs were then given a sufficiently large dose of morphin so they would lie quietly breathing through a Zuntz apparatus. In the cannula a lateral opening was made 1 inch from the trachea, through which samples of air could be taken by sampling-tubes which were previously exhausted for the purpose.

The cannula had two branches, one of which led to the Zuntz apparatus and one branch terminated in a Y tube. One branch of the Y connected with a mercury manometer and the other branch connected with a bottle of known capacity.

A screw clamp was applied to the tube *Z*, which enabled us to produce any desired amount of stenosis.



While the animal was breathing, *S* was closed and a clamp applied at *E*, so the animal breathed only through the Zuntz apparatus.

The bottle to which the tube *B* was connected was then exhausted and the amount of minus pressure in the bottle was accurately measured on the mercury manometer.

When a specimen of alveolar air was wanted, the tube *Z* was clamped at the end of an inspiration. At the same moment the tube *M* was clamped and the clamp at *E* was released. As the signal was given an assistant compressed the animal's thorax and abdomen so the air contained in the lung was aspirated into the bottle as all other communications were closed. During the aspiration it was necessary to clamp the tube *M* to prevent the churning of air by the oscillations of the mercury column. The dog's thorax was also compressed from without during the aspiration process to prevent rupture of the lung, which we found in our first experiments caused pneumothorax.

When the aspiration was completed the clamp at *E* was replaced and the clamps at *M* and *Z* were released, so the animal continued breathing through the Zuntz apparatus.

By measuring the change in the stand of the mercury manometer before and after aspiration we could readily estimate how much air was drawn out of the lungs into the bottle.

By using the same minus pressure in the bottle, we were able to compare the amount of air yielded when there was stenosis, with the amount of air yielded under the same aspiration when there was no stenosis in the respiratory path.

This apparatus was designed for the purpose of getting specimens of alveolar air from dogs. Incidental to these experiments, however, the following observations were made in an experiment designed to measure and analyze the minute volume of air and also to estimate the carbon dioxid content of the alveolar air.

Specimens of alveolar air were procured before a stenosis was produced and also during the period of stenosis. The pressure in the bottle was the same when all the specimens were taken, namely, 290 mm. Hg less than barometric pressure.

Without stenosis, three aspirations yielded 346, 242 and 340 c.c.

With stenosis, three aspirations yielded 405, 610 and 534 c.c.

The increase in the lung volume was not sufficient to cause inspiratory narrowing of the subcostal angle. The subcostal angle distinctly widened during inspiration in the period of stenosis.

Therefore, the increase in the residual air of the dog's lungs was proportionately much smaller than was the increase of residual air in the child who had laryngeal stenosis. We believe we are justified in

arriving at this inference from former comparative observations on the movements of the costal borders in dogs and in human beings.<sup>2</sup>

The patient R. J. exhibited signs during an asthmatic attack which are of interest in this relation. During the night of Aug. 30, 1913, R. J. had an attack of asthma which gave him as much discomfort as any other attacks, but the asthma was confined to the upper left and lower right lobes. The air-hunger was intense and there was both inspiratory and expiratory dyspnea. Coarse râles were abundant over the entire thorax, but fine whistling râles during inspiration and expiration were confined to the upper left and lower right lobes. It was also observed that the right costal border was strongly drawn toward the median line during inspiration, but the left costal border was drawn away from the median line.

Thus far it seems clear we are justified in saying that stenosis anywhere in the tracheobronchial system will cause an increase of the residual air in that part of the lung supplied by the affected air-passages.

This experience also indicates that the excitatory influence operates locally on the affected bronchial system and not by way of the blood-stream. If bronchiolar constriction were accomplished by absorption of split products of proteid into the blood-stream, it is not probable we could have regional bronchiolar constriction with regional increase in pulmonary volume.

The problems of emphysema and asthma are more complicated than first acquaintance would lead one to believe. We can understand how an emphysematous patient may have a bronchiolar spasm and thus contribute to an increase of the residual air; and also, that the same minute volume of respired air with the same respiratory rate will be less effectual than in the non-asthmatic periods.

If the residual air is much increased, then of course the ventilation must be enlarged to maintain a sufficient reduction in the carbon dioxide concentration of the alveolar air. That a greatly increased effort at respiration must be expended by the patient to accomplish this ventilation is clear enough to any one who watches a patient during an attack. When an emphysematous patient has an attack of asthma the minute volume of air and respiratory rate may be unaltered and, indeed, as we will show, the minute volume may be as large as during the interims of comparative comfort, but in spite of the ventilation the patient will be cyanotic during the attack and the carbon dioxide concentration of the alveolar air increases. Whether or not all these facts can be explained by increase of residual air remains to be seen.

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2. Hoover, C. F.: The Functions of the Diaphragm and their Diagnostic Significance, *THE ARCHIVES INT. MED.*, 1913, xii, 214.

CASE 1.—The patient, Mrs. L., was admitted to Lakeside Hospital in April, 1913. The case represented the usual type of emphysema with bronchitis and asthma. Bronchitis existed a year before admission, but asthmatic attacks occurred only a few months before admission.

The tongue, nose, ears and finger-nails showed no cyanosis, although the lips suggested a slight cyanotic tinge. Sputum was abundant and contained many cellular elements. About 40 per cent. of the cells took the acid stain, but the granules of the cells did not have the conformation of the granules of eosinophils. The cells had the appearance of polymorphonuclear cells stained red instead of the usual neutral color.

Curschmann spirals and Charcot crystals were present in great abundance.

Between the attacks, the lungs were sufficiently large to fill the pleural sinuses, but there was distinct inspiratory widening of the subcostal angle.

During the day of April 12, 1913, two specimens of alveolar air were taken and found to contain 5 and 4.55 per cent. of carbon dioxide.

On the night of April 12 the patient had a severe attack of asthma with slight cyanosis. The alveolar air in two specimens contained 5.43 per cent. and 5.3 per cent. of carbon dioxide.

Fifteen minims of epinephrin solution 1:1,000 (adrenalin P., D. & Co.) were then given subcutaneously and in two minutes the air-hunger was relieved and the inspiratory narrowing of the subcostal angle changed to distinct inspiratory widening of the angle. The lower borders of the lung remained the same. Two specimens of alveolar air were then taken and found to contain 4 and 4.10 per cent. of carbon dioxide.

After a number of trials Mrs. L. learned to breathe through the Zuntz apparatus during her asthmatic attacks. We had the opportunity to collect specimens of the minute volume and alveolar air during five attacks of asthma. All the attacks were relieved by the subcutaneous injections of epinephrin so we had the opportunity to compare the lung ventilation and alveolar air during the attacks, with specimens procured directly after the asthma was relieved.

The results obtained on the night of May 1, 1913, are very characteristic and serve to illustrate the question under discussion.

The asthmatic attack was severe. The patient was awakened out of her sleep with air hunger and noisy respiration. Cyanosis was perceptible in the finger-nails and ears and lips. The subcostal angle narrowed during inspiration. The pulse was 100 per minute, respiration 28 per minute, blood-pressure 130 systolic and 90 diastolic.

Four specimens of alveolar air were then taken with the following results: Carbon dioxide. 5.37 per cent.; 5.14 per cent.; 5.20 per cent.; 5.50 per cent.

Immediately after these specimens were taken, a specimen was procured with the Zuntz apparatus.

Time equals .....	seven minutes
Minute volume equals .....	5.06 liters
Respiration rate equals .....	20 per minute
Carbon dioxide equals .....	2.6 per cent.

A second Zuntz specimen was taken with the following result:

Time equals .....	six minutes
Minute volume equals .....	5.2 liters
Respiratory rate equals .....	19.8 per minute
Carbon dioxide equals .....	2.74 per cent.

One hour after the onset of the attack 15 minims of epinephrin solution 1:1,000 given subcutaneously without clearly perceptible improvement in the symptoms. Twenty minutes later 15 minims of epinephrin 1:1,000 were again given subcutaneously. A few minutes later the asthma subsided and the costal angle changed from narrowing to widening during inspiration.

A Zuntz specimen was then taken.

Time equals .....	eight minutes
Minute volume equals.....	6.4 liters
Respiratory rate equals.....	17.6 per minute
Carbon dioxid equals.....	2.0 per cent.

Three specimens of alveolar air were then taken with the following results: Carbon dioxid, 5.2 per cent., 5.07 per cent., 5.01 per cent.

In all the experiments tried on this patient there was not sufficient change in the minute volume of air and carbon dioxid concentration during the attacks of asthma to account for cyanosis. It seems there must have been some other factor besides a change in the ventilatory function of the lung to account for cyanosis during the attack of asthma.

CASE 2.—Patient, R. J., a colored man, aged 30, had emphysema, bronchitis and asthma during four years before entering Lakeside Hospital. During July, 1913, R. J. had twelve attacks of asthma which were relieved by subcutaneous injections of epinephrin. During August the attacks continued much the same.

August 29, specimens were taken when the patient was breathing very comfortably, although he had an asthmatic attack the previous night. Four specimens of alveolar air were taken and gave a carbon dioxid content of 6.6 per cent. 6.5 per cent., 6.9 per cent. and 6.3 per cent. The respiratory rate was 16 per minute; minute volume was 9.180 liters.

Aug. 30, 1913, R. J. had a severe attack of asthma with intense air hunger. During the asthma the alveolar air gave the following result in carbon dioxid: 7.1 per cent., 7.9 per cent., 7.6 per cent. The respiratory rate was 25.6 per minute; minute volume was 9.570 liters.

This attack began at 7 p. m. At 7:29 p. m., 15 minims of epinephrin were given subcutaneously. Air hunger ceased very suddenly at 7:34 p. m. Alveolar air specimens, taken directly after asthmatic breathing ceased, had the following content of carbon dioxid: 6.1 per cent., 5.7 per cent. and 6.2 per cent. The respiratory rate was 21 per minute. The minute volume was 9.6 liters.

The notable fact in this observation is that during the asthmatic attack the minute volume was nearly as large as when the attack was over and the respiratory rate was increased only four per minute during the attack. During the asthmatic period there was cyanosis of the tongue.

Sept. 4, 1913: Asthma severe, loud whistling râles during inspiration and expiration throughout the lungs. The subcostal angle narrows during inspiration. Three alveolar air specimens had a carbon dioxid content of 5.7 per cent., 6.6 per cent. and 6.6 per cent.

Two Zuntz specimens were taken during the attack of asthma with the following results: 1. Time, five minutes; respiratory rate, 24.2 per minute; minute volume, 6.610 liters. 2. Time, five minutes; respiratory rate, 22 per minute; minute volume, 6.58 liters.

After the preceding specimens were taken, 20 minims of 1:1,000 epinephrin were given subcutaneously and relief followed immediately.

Two specimens of alveolar air were then taken and they contained 5 per cent. and 5.9 per cent. of carbon dioxid.

A Zuntz specimen (taken directly after the attack) gave the following:

Minute volume equals.....	7.772 liters
Respiratory rate equals.....	23 per minute
Carbon dioxid equals.....	1.54 per cent.

The attack of September 4 was particularly severe and the patient's suffering was intense, but judging from the pulmonary ventilation and the carbon dioxid content of the alveolar air one is at a loss to account for the source of cyanosis, for during the attack the carbon dioxid content of the alveolar air was raised only 0.6 per cent. and the minute volume was diminished only



one liter. This increase of the carbon dioxid concentration with the lowered minute volume and increased residual air, may account for great discomfort, but these factors do not account for cyanosis during the attack.

Sept. 18, 1913, R. J. had an asthmatic attack of moderate severity. The lower lung filled the pleural sinuses and the subcostal angle narrowed during inspiration, but there was no cyanosis.

During the attack two Zuntz specimens were taken.

1. Time, four minutes; minute volume, 9,790 liters; respiratory rate, 25 per minute.

2. Time, five minutes; minute volume, 9,870 liters; respiratory rate, 25.6 per minute.

Two specimens of alveolar air contained 5.96 per cent. and 5.65 per cent.

Epinephrin given subcutaneously relieved this attack in less than one minute. The subcostal angle widened during inspiration.

Two Zuntz specimens then taken gave the following results:

1. Time, three minutes; minute volume, 9,000 liters; respiratory rate, 21.6 per minute.

2. Time, five minutes; minute volume, 8,790 liters; respiratory rate, 22 per minute.

3. The three alveolar specimens gave the following in content of carbon dioxid: 5.22 per cent., 4.74 per cent. and 5.44 per cent.

October 12, R. J. had a severe attack of asthma with cyanosis.

Two Zuntz specimens were taken. Results were:

1. Time, six minutes; minute volume, 7.04 liters; respiratory rate, 25.5 per minute.

2. Time, five minutes; minute volume, 7.37 liters; respiratory rate, 26.4 per minute.

Two alveolar air specimens gave content of carbon dioxid: 8 per cent. and 6.88 per cent.

The specimens given above are some of the most satisfactory we could procure from these patients. Although we do not believe the Zuntz method has proved to be satisfactory for accurate studies of the carbon dioxid content of expired air, the results are valuable for comparing asthmatic breathing with the breathing during interims of comfort.

The results show that during asthmatic attacks the minute volume of air and respiratory rate may be little altered. The difference would be scarcely enough to cause discomfort in a normal person. It was also observed that the percentage of carbon dioxid in the alveolar air was not much increased, but the increase in percentage of carbon dioxid in the alveolar air was much greater than the difference in the minute volume would allow.

Provided that the minute volume of air remained unaltered, there would be a rise in the carbon dioxid concentration of alveolar air because the residual air is increased, and for this reason the same volume of ventilation would cause less reduction in the concentration of carbon dioxid in the alveolar air. We find, however, that the dilution of residual air is not directly proportioned to the amount of air inhaled.

If we assume the residual air in the lungs of a normal person to be about 2 liters we are justified in assuming that at the end of a forced expiration the residual air is constant in amount. In a large number of observations on a healthy man, G., it was found if a forced expiration was made and then followed by a maximum inspiration and a forced expiration, and the total expired air was measured, the total expiration did not vary more than 300 c.c. in any of the trials.

If the maximum ventilation remains constant then we are justified in assuming that the amount of alveolar air in the lungs and bronchial tree at the end of a maximum expiration will be the same or very nearly the same.

We found in G. that the amount of carbon dioxide eliminated per minute when he was at rest varied between 415 and 430 c.c. (moist).

While breathing tranquilly, seated, G. made a forced expiration lasting one second. The alveolar air at the end of the expiration contained 6.06 per cent. carbon dioxide. G. then inspired two seconds and then made a forced expiration lasting two seconds.

The total expiration was captured and a specimen of the end alveolar air was taken at the same time. Briefly stated, the following results were obtained:

Expiration, one second, alveolar air equals.....	6.06 per cent. carbon dioxide
Inspiration .....	two seconds
Expiration, two seconds, alveolar air equals.....	5.80 per cent. carbon dioxide
Total alveolar air equals .....	735 c.c.
Dead space equals .....	140 c.c.
Total expiration equals .....	875 c.c.
Carbon dioxide content equals .....	4.88 per cent.

During the four seconds occupied in the inspiration and expiration 27.8 c.c. of carbon dioxide were secreted.

Assuming there was no carbon dioxide secreted during the four seconds and also taking 2,000 c.c. for the residual alveolar air, at the end of the first expiration there must have been a minimum of (2,000 + 140) c.c. times 6.06 per cent. of carbon dioxide in the alveolar air and dead spaces.

At the end of the inspiration the alveolar air in the lung with its carbon dioxide dilution can then be expressed by  $2,000 + (875-140) x$ .

We then have the following formula:

$$2,140 \times 6.06 \text{ per cent.} = 2,735 \times x.$$

Therefore  $x$  or the concentration of carbon dioxide in the alveolar air would have been 4.74 per cent. had there been no excretion of carbon dioxide during the four second's interval.

The carbon dioxide excreted during the interval of four seconds was 27.8 c.c. which is 1.01 per cent. of the amount of air in the alveolae at the end of inspiration. This amount was 2,735 c.c.

If this be added to the supposed percentage of 4.74 per cent. we have 5.75 per cent., which is within 0.05 per cent. of the result obtained, namely, 5.80 per cent. This result was obtained with an inspiration of 875 c.c. What is the dilution when larger amounts are inspired?

G. expired one second, alveolar air = 6.23 per cent. carbon dioxid; inspired three seconds, then expired two seconds. Result:

Total expired air equals.....	2.810 c.c.
Carbon dioxid in expired air equals	4.12 per cent.
Alveolar air equals.....	5.09 per cent. CO <sub>2</sub>
Total alveolar air equals.....	2.274 c.c.
Dead space equals.....	536 c.c.

We will not occupy space here to discuss the problem of the dead space, as that will be treated in a publication elsewhere. It will suffice for the present to say that the dead space is not enlarged, so we will retain the dead space as 140 c.c. Assuming the maximum excretion of 35.8 c.c. of carbon dioxid to have been the amount excreted during the interim of five seconds, we should have had a carbon dioxid content of 3.61 per cent. instead of 5.09 per cent., as we really found. The larger the inspiration in a normal lung the less effective (proportionately) the ventilation becomes; that is, the less effective (proportionately) is the carbon dioxid of the residual air diluted.

Therefore, the same minute volume of ventilating air will be less effective in an emphysematous lung, not merely because there is a larger amount of residual air to be diluted, but also because the diffusion of carbon dioxid is less effective in an enlarged infundibular space.

One supposes that in lung ventilation there is a sharp definition histologically and functionally between the dead-space air and the alveolar air which is in contact with the respiratory membrane. We would also suppose that the alveolar air (or air which is in contact with the respiratory membrane) being divided among several million chambers would have a uniform carbon dioxid content within a second's time after a maximum inspiratory effort. This is, however, not the case as we believe we have shown in several ways.

This diminishing effectiveness of ventilation in overdistended lungs is responsible for the apparent increase of the dead space in forced breathing while at rest and during exercise. It is a large factor in the limitations of endurance in physical exercise. It also is a large factor in the failure to reduce the carbon dioxid concentration of alveolar air in emphysema and asthma when the minute volume of air is mathematically adequate for the purpose.

The increased amount of residual air and enlargement of the alveolar spaces and bronchiolar narrowing will account for most of the symptoms in asthma, but there is often an inconsistency between cyanosis and the carbon dioxid percentage of the alveolar air.

As we have observed above, we can account for the increased carbon dioxid concentration in the alveolar air when there is little or no diminution in the minute volume of air, but there is another notable fact in asthma, namely, the very moderate increase in the percentage of carbon dioxid in the alveolar air when the patient is cyanotic.

Patient 1, Mrs. L., had cyanosis of the lips, finger-nails and ears during her attacks of asthma when the carbon dioxid of the alveolar air was not above 6 per cent.

R. J., the second patient, had on two occasions only a sufficiently high carbon dioxid content of his alveolar air to account for cyanosis. These days were August 30 and October 12, when the alveolar air had a carbon dioxid content of 7.6 per cent. and 8 per cent. These occasions are consistent enough. As we have found in emphysematous patients without asthma, the alveolar air must attain at least 7 per cent. carbon dioxid before the patient becomes cyanotic. Asthmatic patients have cyanosis with a carbon dioxid content of their alveolar air, which is not high enough to cause cyanosis in emphysema uncomplicated with asthma. How can this difference in the two conditions be explained? We cannot account for the difference in cyanosis in the two conditions on the basis of ventilatory function. It seems there must be an additional cause which requires an explanation. As was stated in the first pages of this discussion, we were unable to find any indications of an impairment in the minute volume of blood through the pulmonary circulation, but may there not be an increased content of blood in the respiratory vessels which could impair the function of external respiration, so we would then have the additional factor of impaired respiratory function added to the impaired ventilatory function?

The patient R. J. had an attack Aug. 30, 1913, which was attended with a distinct increase of carbon dioxid in the alveolar air. During the asthma the alveolar air carbon dioxid, in three specimens, was 7.1 per cent., 7.9 per cent. and 7.6 per cent. After epinephrin was given, three specimens contained 6.1 per cent., 5.7 per cent. and 6.2 per cent. of carbon dioxid.

After the attack the minute volume measured only 100 c.c. more than during the attack of asthma with cyanosis. This difference is of course negligible so far as ventilation of the lung is concerned. Increased residual air would not have been so large a factor because in this attack the evidences of bronchiolar stenosis were limited to the right lower lobe and the left upper lobe.

Bedside notes made at the time, describe the lower right lung border at the eighth, tenth and twelfth ribs, in the midclavicular, axillary and subcostal lines of the right side, and at symmetrical points on the left side, the lower lung border was at the sixth, eighth and tenth

ribs. The right costal border was drawn toward the median line during inspiration and the left costal border was drawn away from the median line during inspiration. The disparity in movement of the lower portions of the two lungs was so great that the notes describe the excursion of the thorax as presenting the appearance of inspiratory torsion of the lower thoracic regions. During the asthmatic attack the patient coughed up a lot of foamy blood-stained sputum. There were no signs of stasis in the heart, veins or liver, and the attack was completely relieved by a subcutaneous injection of 15 minims of 1:1,000 epinephrin.

It was this experience which first gave rise to the suspicion that hyperemia of the pulmonary vessels was a factor in the cyanosis of asthma.

Dec. 7, 1913, R. J. had another experience which was significant in this relation. He had an attack of asthma which seemed not unlike his former attacks. The signs of bronchiolar spasm were relieved by epinephrin, but he continued with his lamentations when the lung was no longer increased in volume sufficiently to cause inspiratory narrowing of the subcostal angle. There was no evidence of obstruction to inspiration. Expiration was much prolonged and the patient complained bitterly of great distress in the substernal region. In reply to our questions he said there was no pain, but he constantly complained of what he termed "a misery." There were no fine whistling râles in the lungs, but there was an abundance of coarse mucous and sonorous râles during inspiration and expiration.

The blood-pressure measured 175 systolic and 103 diastolic. Apomorphin  $\frac{1}{20}$  grain was then given subcutaneously. This was followed directly by vomiting. The blood-pressure dropped to 123 systolic. The diastolic pressure could not be determined. The patient was perfectly comfortable and in about ten minutes he was sound asleep. This relief came after his distress had lasted many hours and repeated injections of morphin had failed to give any relief. Apomorphin was given on this occasion, not because it was believed there was any need of lowering the aortic pressure to relieve signs of incompetence of the left ventricle, but to procure the revulsant effect of dilatation of the splanchnic vessels.

The pathological physiology in this whole play of symptoms is not clear, but the whole course of the trouble looked very much as though hyperemia of the pulmonary vessels was the cause of the distress after bronchiolar spasm ceased.

In a former publication<sup>3</sup> it was suggested that an enlargement of the dead space may be partly responsible for the ineffective ventilation of

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3. Hoover, C. F.: *The Minute Volume and Alveolar Air in Pulmonary Emphysema*, *THE ARCHIVES INT. MED.*, 1913, xi, 52.



emphysematous lungs, but since then our further studies prove the dead space in emphysema is not enlarged. The increase of residual air and hyperdistention of the infundibula are the two causes for the high carbon dioxid content of alveolar air in emphysematous patients. Keith<sup>4</sup> (quoting Oppel's work) says, "If out of a rubber balloon a model of the terminal bronchiole and infundibulum and alveoli be made and inflated, it is the central or infundibular space which expands most, the alveoli implanted on its walls being widened, but at the same time rendered more shallow. The point which one seeks to emphasize is that it is not the alveoli but the infundibula that should be regarded as the essential expansile parts of the lung. The larger and more plentiful the infundibula in a part of the lung, the more readily will that part respond to any distending force." This anatomical conception is quite consistent with the results of our studies in lung ventilation, but when we consider that an infundibulum has a diameter of not more than 1 mm., and that in hyperdistention the infundibula of normal lungs cannot be enlarged more than 2 or 3 mm., it seems astonishing that when 2 liters of air distributed in such small chambers are diluted with the addition of 3.5 liters, the diffusion of gases are not uniform throughout the entire mass.

This is, however, a fact and our failure to recognize this in the past has led to several false conceptions of ventilation of normal lungs and lungs affected with emphysema and asthma.

When G., a normal man, breathed tranquilly into a rubber bag for five minutes at the rate of 15 respirations per minute, the total expiration was 52,310 c.c.; the minute volume was 10,462 c.c.; each respiration was 697 c.c.

Two specimens of air taken from the total expired air contained 3.97 per cent. and 4.01 per cent. of carbon dioxid. His alveolar air contained 6.0 per cent.

Sam G., a patient who had severe emphysema without any signs of obstruction in his bronchial tree, breathed tranquilly at rest two minutes and breathed 45 times in the two minutes, the total expiration was 22,500 c.c.; the minute volume was 11,250 c.c.; each inspiration was 501 c.c.

The minute volume or expired air contained 4.74 per cent. and 4.61 per cent. carbon dioxid in two specimens.

Two specimens of the alveolar air, taken during the collection of the expired air, contained 7.17 per cent. and 7.44 per cent. carbon dioxid.

Sam G. had pronounced cyanosis, and although his minute volume of expired air was greater than that of G., Sam G. did not dilute the

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4. Keith: In *Further Advances in Physiology*, Leonard Hill, p. 186.

carbon dioxid of his alveolar air nearly so well as did G. The dead space, however, as measured on the basis of the difference in carbon dioxid concentration in the alveolar and total expired air, showed the dead space in the two men to be practically the same. The dead space in both measured between 150 and 165 c.c. The dead spaces in the two men were measured a great many times when they were breathing tranquilly and we never found the dead space enlarged in the emphysematous man, nor did we find the dead space enlarged in two other emphysematous patients whose minute volume air and alveolar air were examined many times.

It was shown in a former publication<sup>3</sup> how an emphysematous patient was cyanotic on one occasion when his minute volume of air and respiratory rate were the same as on a subsequent occasion when his emphysema and cyanosis and carbon dioxid concentration in the alveolar air had all diminished. In other words, the minute volume and respiratory rate remaining the same, when emphysema appears the patient will be cyanotic and the alveolar air carbon dioxid percentage will be raised. It seems by exclusion and direct evidence we may say that the real difficulty of ventilation in emphysema and asthma lies in the distention of the infundibula, and this fails to allow an equal diffusion of carbon dioxid throughout the alveolar air.

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# EFFECT OF INTRAVENOUS AND INTRASPINAL TREATMENTS ON CEREBROSPINAL SYPHILIS \*

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With the demonstration by Noguchi<sup>1</sup> of *Spirochaeta pallida* in the central nervous system tissues, and with the successful use of salvarsan, paresis and locomotor ataxia have become less matters of purely neurological concern and more problems of infection, immunity and chemotherapy. Under this aspect the syphilitic disturbances of the central nervous system function have taken on a new interest alike for the student of immunity, the clinician and the psychologist. For it is now clear that the symptoms of central nervous system syphilis, be they pain, ataxia, or psychic disturbance, depend, as is the case in acute poliomyelitis, on the location of the damaging lesions.

The therapeutic problem, therefore, is fundamentally of a similar nature to that found in any infection in which the specific agent is sent to destroy the infecting organism. The agent and organism must be brought into contact. The well-known impermeability of the choroid plexus to foreign substances renders the access of parenterally given drugs to the brain and cord difficult; consequently, it is to be inferred that salvarsan, when it is introduced into the blood-stream, comes in very minute quantities, if at all, into contact with spirochetes, lying within the meninges or in the outer layers of the brain. It has been shown, however, that the choroid membranes can be rendered more passable by injury or inflammation. Furthermore, Flexner<sup>2</sup> has demonstrated that immune serum may be introduced most effectually in certain bacterial infections of the meninges. Purposing to bring the largest possible amount of salvarsan in contact with the brain and cord, numerous workers have employed each or both of the principles just mentioned. Sicard has argued most urgently that in the damaging effect of the spinal injections lies their real importance. To accomplish this end he has injected 5 c.c. of a 0.5 per cent. sodium chlorid solution intracortically through a small trephined opening in the skull. Twenty-four hours later he has given an intravenous injection of salvarsan. Robertson<sup>3</sup> in Edinburgh was perhaps the first to

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1. Noguchi and Moore: Jour. Exper. Med., 1913, xvii, 232.

2. Flexner and Jobling: An Analysis of Four Hundred Cases of Epidemic Meningitis Treated with the Antimeningitis Serum, Jour. Am. Med. Assn., 1908, li, 269.

3. Robertson: Edinburgh Med. Jour., 1913, x, 428.

use salvarsanated serum by intraspinal injection, but his cases were not followed over a definite period of time and the reports are not complete.

During the past year a considerable amount of work has been done by the French, especially Marinesco,<sup>4</sup> Levaditi,<sup>5</sup> Marie,<sup>6</sup> Jeanselme, Vernes, Bloch,<sup>7</sup> Ravaut,<sup>8</sup> Sicard and Riley. These workers, as well as Wechselmann,<sup>10</sup> in Germany, have given intraspinal injections of neosalvarsan in solution. Some have used as high as 10 or 12 mg. at a dose. None of the cases have been followed over a sufficient period of time, however, and the reports are very incomplete. In almost all of the cases there were serious symptoms of an undesirable nature, the most prominent of these being retention of urine. Many of the patients also had convulsive attacks following injection. Most of the work was done on patients suffering from general paresis. In general it may be said that the reports of all these observers are limited in detail and the results did not seem to warrant the rather severe symptoms which many have reported. The scope of this paper does not permit a report of the work of the various authors but a full bibliography is given in the footnotes. By far the most careful work on the subject of treatment of syphilis of the central nervous system by intraspinal injection is that of Swift and Ellis.<sup>11</sup> These authors report a series of twenty cases which have been followed for a year or more with improvement in symptoms and serological findings resulting from treatment.

The present work may be considered as merely a continuation of their series, for, with certain minor modifications necessitated by circumstances arising outside of institutional control, the technic and methods of management are those described by them.

Twenty-five cases have been selected for presentation. Symptomatically they have been arranged so that pain predominates at one end of the series and psychic disturbance at the other. Cytologically and serologically they cannot be classified profitably. These two factors

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4. Marinesco: *Ztschr. f. diätet. u. physik. Therap.*, 1913, xvii, 194; Marinesco and Minea: *Bull. de l'Acad. de méd.*, 1914, lxxvi, 259.

5. Marie and Levaditi: *Bull. et mém. Soc. d. Hôp.*, 1913, xxix, 675.

6. Levaditi, Marie and Martel: *Soc. de Biol.*, 1913, lxxv, 567.

7. Jeanselme, E., Vernes, A., and Bloch, M.: *Du traitement des femmes syphilitiques enceintes par le salvarsan*, *Bull. et mém. Soc. d. Hôp.*, 1913, xxix, 792.

8. Ravaut: *Bull. et mém. Soc. d. Hôp.*, 1913, xxix, 752.

9. Sicard and Reilly: *Bull. et mém. Soc. d. Hôp.*, 1913, xxix, 861.

10. Wechselmann: *Deutsch. med. Wchnschr.*, 1912, xxxviii, 1446.

11. Swift, Homer F., and Ellis, Arthur W. M.: *The Treatment of Syphilitic Affections of the Central Nervous System with Especial Reference to the Use of Intraspinal Injections*, *THE ARCHIVES INT. MED.*, 1913, xii, 331.

led to the expression of the analogy to poliomyelitis, namely, that it is not the nature of the infection so much as the location that determines the symptoms in central nervous syphilis. These twenty-five patients were all treated intensively for active syphilis. All but one received combined intravenous and intraspinal injections. Mercury and potassium iodid were also used, but the chief reliance and interest were centered on the action of salvarsan, neosalvarsan and salvarsanated serum.

Intravenously most of the patients were treated at weekly intervals with doses of salvarsan varying from 0.3 to 0.6 gm., or neosalvarsan in full doses. Salvarsan was the drug of choice and was changed for neosalvarsan only when the patient had an anaphylactic reaction. The usual technic in the preparation of doses was observed. Intraspinally most of the cases received 30 c.c. of 50 per cent., or from 20 to 25 c.c. of full-strength serum, separated by centrifugalization from blood withdrawn forty minutes after the intravenous dose of salvarsan. The serum was heated to 56 C. and was introduced intraspinally the same day. Lately several patients have been bled before the intravenous dose, and then salvarsan up to a milligram added *in vitro* to the serum. This mixture was heated to 37.5 C. for forty minutes, and then 56 C. for half an hour. No serious symptoms followed any of the injections. Some patients had increase of pain for a few hours following the injection. This, however, could usually be controlled by phenacetin, caffein and codein. Occasionally morphin was used. Once spinal fluid was removed by puncture fourteen hours after treatment to relieve the pain. Recently, however, there has appeared in several cases a subjective feeling of numbness of the feet and legs, usually below the knee, but in some cases reaching to the hips and involving the perineum. Cutaneous sensation is not impaired. The symptom has occurred with one exception in patients who received serum salvarsanated *in vitro*. It seems probable, however, that there is a definite association between treatment with this form of serum and the symptom of numbness. The patients have noticed no discomfort at the time of treatment and have first complained of the numb feeling after three or four injections have been given. Not all patients who have received directly salvarsanized serum have shown the symptom, and none have had the bladder disturbance described by those who have injected salvarsan into the dural sac. In a recent publication Gennerich<sup>12</sup> has noted symptoms not unlike those which have been described here in patients to whom he has given neosalvarsan intraspinally.

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12. Gennerich: München. med. Wchnschr., 1914, lxi, 823.



Another unsatisfactory event which is unassociated apparently with serum directly salvarsanized, but which has been seen in patients treated by both methods, is the sudden increase of ataxia following a period of definite improvement. If all treatment is stopped in these cases and rest with massage and increasing educational exercises is instituted the ataxia improves fairly rapidly. This phenomenon is especially striking in Case 96; for after the spinal fluid findings had returned to normal and the patient felt extremely well and encouraged, there was a sudden onset of ataxia, worse than any he had previously experienced. Case 76 behaved in a similar manner.

The cases have been grouped according to symptoms and not according to their spinal fluid findings, because it was found that spinal fluid changes varied very greatly in all the groups, and no classification was possible.

#### GROUP I: CASES WITH PAIN

The first group of cases is composed of those individuals who complained of pain. Three of them had no ataxia; one had a very slight Romberg sign. Their physical signs were typical of the condition known as locomotor ataxia, as regards pupils, reflexes and sensory disturbances, with the exception of one woman whose knee-jerks were exaggerated.

CASE 49.—W. A. F., man, aged 45; chancre twelve years ago; no secondaries; very small amount of treatment; perfectly well until 1912 (two years ago); then numbness of great toe followed by slight unsteadiness, giving trouble in running or walking; shooting pains in the testicles; girdle sensation; shooting pains in the legs.

*Physical Examination.*—Pupils a little sluggish; knee-jerks and Achilles jerks absent; Romberg sign present.

*Spinal Fluid.*—Clear, pressure normal; 25 cells; globulin  $\pm$ , Wassermann negative throughout. Patient was given a series of intravenous injections of salvarsan, no intraspinal; marked improvement.

CASE 17.—J. L., woman, aged 56; doubtful miscarriage; two children; no knowledge of infection; no secondaries; tremendous pain in arm and fingers; less in legs and toes.

*Physical Examination.*—Pupils unequal, small, irregular, Argyll Robertson; reflexes upper and lower all exaggerated; sensation, pain slightly diminished.

*Spinal Fluid.*—Clear, pressure low; cells 37; globulin +++; Wassermann +++ in 0.3 c.c.; patient treated intensively by intravenous and intraspinal injection; at the end of four months pains much less.

*Spinal Fluid.*—Clear; pressure low; cells 5; globulin-Wassermann ++ in 0.5 c.c.

CASE 126.—Dr. L., aged 48. Suffering abdominal pain for the past two or three years; occasional pains in legs. No knowledge of infection; no secondaries.

*Physical Examination.*—Pupils small, equal; Argyll Robertson; knee-jerks and Achilles jerks absent; sensation, diminution of pain sense over the lower legs.

*Spinal Fluid.*—Clear, pressure increased; cells 52; globulin ++; Wassermann +++ in 0.1 c.c.; blood-serum ++. At the end of four months marked improvement in symptoms. No change in physical signs. Spinal fluid clear, pressure slightly increased; cells 0; globulin ++; Wassermann +++ in 0.5 c.c. Blood-serum negative; severe dermatitis; treatment suspended.

CASE 76.—J. P. L., man, aged 32, chancre seven years ago; well treated; mercury; no secondaries; for the last five or six years pains in legs; increasing ataxia.

*Physical Examination.*—Pupils small, Argyll Robertson; reflexes, knee-jerks and Achilles jerks absent; sensation, scattered areas of loss of touch and pain; Romberg sign moderately marked.

*Spinal Fluid.*—Clear, pressure normal; cells 40; globulin ++; Wassermann ± in 0.3 c.c., +++ in 0.5 c.c. Blood serum +++. Patient given intensive treatment for three months at which time symptoms somewhat improved.

*Spinal Fluid.*—Twenty-two cells; globulin ±; Wassermann +++ in 0.5 c.c. Intraspinial treatment begun. Spinal fluid, after three treatments, 5 cells; globulin ++; Wassermann + in 0.5 c.c.; blood-serum ++; sudden increase of ataxia.

#### GROUP II: CASES WITH PAIN AND ATAXIA

The second group of cases comprises text-book examples of locomotor ataxia, cases in which pain, ataxia and physical signs are well marked.

CASE 103.—S. H. P., man, aged 37; chancre (?) treatment (?). Patient had great pain in legs and very marked ataxia.

*Physical Examination.*—Pupils irregular; react slightly to light and accommodation; knee-jerks and Achilles jerks absent; areas of analgesia about abdomen, back and feet.

*Spinal Fluid.*—Cells 110; globulin ++; Wassermann + in 0.5 c.c. Patient received a series of four injections of neosalvarsan, followed by a long series of mercury for two months, at the end of which time spinal fluid had 7 cells; moderate globulin; Wassermann negative. He then received six more injections of salvarsan, followed by another series of mercury. He went away for the summer. Three months later spinal fluid showed 41 cells; globulin ±; Wassermann + in 0.5 c.c. He was treated again intravenously and given two intraspinal treatments. These caused very great pain and were discontinued. Patient given intravenous treatment five times, at the end of which time spinal fluid had 8 cells; globulin normal; Wassermann negative. No further treatment for two months. Puncture done again, showed 8 cells; globulin ±, Wassermann doubtful in 0.5 c.c. This case suggests very strongly that the intravenous treatment alone was insufficient.

CASE 128.—O. T. S., man, aged 53. Chancre thirty years ago; mild secondaries; well treated with mercury; pains began ten years ago; has had one intramuscular and three intravenous injections of salvarsan.

*Physical Examination.*—Ptosis of left lid; pupils Argyll Robertson; slight pallor of disk; knee-jerks and Achilles jerks absent; sensation disturbed.

*Spinal Fluid.*—Faintly blood-tinged; pressure increased; 22 cells; globulin ++; Wassermann ++ in 0.3 c.c.; blood-serum + in 0.2 c.c. Duration of treatment five and one-half months; sixteen intravenous and six intraspinal injections; the latter always caused pain. Patient improved after the first three, then began to go down hill; became melancholic, considerably depleted; terminal bronchopneumonia.

CASE 93.—J. S., aged 42, no chancre, no secondaries; gonorrhea two or three times; three years ago numbness in the feet; six months ago trouble in walking; has improved since; has had two doses of salvarsan and mercury rubs.

*Physical Examination.*—Pupils pin-point, do not react; knee-jerks absent; sensation disturbed, chiefly hyperesthesia; Romberg marked.

*Spinal Fluid.*—Three hundred and seventy-five cells; globulin +; Wassermann +++ in 0.1 c.c. Patient had treatment for twelve months with some intermissions; improved considerably.

*Spinal Fluid.*—Pressure normal; cells 20; globulin +; Wassermann + in 0.5 c.c. Physical signs not changed; pain following intraspinal treatment.

CASE 94.—T. W. S., man, aged 34. Chancre fifteen years ago, no treatment; pain, ataxia, loss of weight.

*Physical Examination.*—Pupils Argyll Robertson, mid-wide, knee-jerks and ankle-jerks absent; sensation touch and pain gone over the feet and legs; marked ataxia.

*Spinal Fluid.*—Clear, pressure low, cells 131. globulin +; Wassermann ++ in 0.3 c.c. Patient under treatment for ten and a half months; nineteen intravenous and three intraspinal injections. The latter always caused pain; once puncture had to be done fourteen hours after treatment to relieve pain. Very marked improvement; patient gained weight. Spinal fluid pressure normal; 5 cells; globulin ±; Wassermann negative.

CASE 21.—J. M. D., man, aged 54. Chancre twenty-nine years ago; slight secondaries; disappeared rapidly; well ever since; five years ago pains; marked ataxia; morphinism.

*Physical Examination.*—Pupils small; Argyll Robertson present; knee-jerks and Achilles jerks absent; sensation, pain lost below level of nipples; marked Romberg sign.

*Spinal Fluid.*—Clear, pressure increased; cells 62; globulin ++; Wassermann negative. Patient given six injections of salvarsan, one intraspinal. Spinal fluid: cells 21; globulin ++; Wassermann negative; very severe pain following last treatment; took 4 grains of morphin during the night; has not reappeared.

CASE 89.—M. D., man, aged 46. Gonorrhea eighteen years ago; two months later rash; treated with inunctions for three weeks, since then nothing. Seven years ago began to have pains which have persisted ever since; ataxia.

*Physical Examination.*—Pupils unequal, one Argyll Robertson, the other reacts slightly to light. Knee-jerks and Achilles jerks absent; also biceps and triceps.

*Spinal Fluid.*—Clear, pressure low; cells 66; globulin +; Wassermann ++ in 0.3 c.c. Patient has been under treatment one and one-half months; has had seven intravenous and four intraspinal injections; pain becoming less. Spinal fluid: cells 8; clear; pressure low; globulin +; Wassermann +++ in 0.5 c.c. Patient is a moderate morphinist.

#### GROUP III: ATAXIA WITHOUT PAIN

The third group is made up of those patients who have a simple ataxia and no pain. The physical signs of these cases were also almost typical.

CASE 95.—W. S. P., man, aged 47. Gonorrhea twenty-three years ago, no chancre, no secondaries; seven years ago had an ulcer on the leg, the result of injury, but it was said subsequently to be syphilitic. Four months ago patient fell and struck his head; unconscious for four hours; three weeks later noticed

weakness in legs, lack of control, no pain; recently slight circular pain about the waist; slight emotional disturbance; instability.

*Physical Examination.*—Pupils equal; react to light; sensation, pharynx anesthetic, diminution of touch and pain over the arm and round right elbow, and over heart-shaped area over end of spine.

*Spinal Fluid.*—Clear, pressure not increased; cells 51; globulin +; Wassermann ++ in 0.5 c.c. Patient given several injections of mercury before salvarsan was started; has been under treatment four and one-half months; sixteen intravenous injections, at the end of which time spinal fluid had 5 cells; globulin  $\pm$  to +; Wassermann + in 0.5 c.c. Since then he has been given two intraspinal injections. Spinal fluid clear; pressure normal; cells 10; globulin  $\pm$ ; Wassermann + to ++ in 0.5 c.c. Patient is very much steadier, is able to work all day and feels a great deal better.

CASE 96.—W. A. F., man, aged, 36. Father died of paresis. Seven years ago soft chancre; no treatment; no secondaries; two years ago became talkative; since then nothing; past two or three months unsteadiness in walking.

*Physical Examination.*—Pupils equal, regular. Argyll Robertson; knee-jerks and Achilles jerks absent; sensation normal. Romberg sign; very slight general tremulousness; seems to be very slightly dull mentally.

*Spinal Fluid.*—Clear; pressure slightly increased; cells 133; Wassermann +++ in 0.3 c.c.; blood-serum +++. Patient started with mercury; then given ten intravenous and five intraspinal injections. Patient remarkably improved; mental dulness disappeared; ataxia still marked. Spinal fluid: clear; pressure normal; cells 6; globulin ++; Wassermann — in 0.5 c.c.

CASE 124.—P. S. P., man, aged 36. Soft chancre eleven years ago, no secondaries; no treatment; ten months ago unsteadiness in feet, increasing; at present extreme ataxia, very little pain.

*Physical Examination.*—Pupils Argyll Robertson, Romberg marked.

*Spinal Fluid.*—Clear, cells 11; pressure normal; globulin +; Wassermann ++ in 0.1 c.c. Patient has had six injections of salvarsan and four intraspinal treatments. No change yet in symptoms, except perhaps increase in ataxia.

*Spinal Fluid.*—Clear, cells 11; pressure normal; globulin +; Wassermann +++ in 0.5 c.c.

#### GROUP IV: CASES WITH OPTIC ATROPHY

The fourth group consists of those most distressing cases of failing vision, due to optic atrophy. The strange thing about them is that, notwithstanding extreme changes in spinal fluids and other evidences of syphilitic disease of the central nervous system, the patients have been absolutely unconscious of anything amiss except increasing blindness. Some forms of syphilitic meningitis indeed seem to be compatible with years of comparative health. In cerebrospinal syphilis the spinal fluids with increased cells and heavy globulin content indicate inflammation of the meninges. Optic atrophy in these cases is due, according to Stargardt<sup>13</sup> to the pressure of exudates on the nerves. According to this view, then, the final state of vision following treatment depends on whether or not pressure can be removed before nerve atrophy has set in. From the patients' point of view these

13. Stargardt: Arch. f. Psych. u. Nervenkr., 1913, li, 711.

cases have been disappointing except in one very early case. From the point of view of effect on the infection of the central nervous system, as shown by the spinal fluid changes, treatment is fairly satisfactory.

CASE 91.—J. N. W., man, aged 40 years. Gonorrhea, twenty years ago, again three years ago; no knowledge of chancre, no secondaries; double vision ten years ago; three years ago Argyll Robertson pupil discovered accidentally; Wassermann negative, no treatment. One year ago again eye change was accidentally discovered and the patient was immediately put on mercury; has been having mercury off and on ever since. Patient experiences no discomfort of any kind, except that he is intensely nervous and energetic.

*Physical Examination.*—Pupils unequal, reaction to light absent, except perhaps a very slight movement in the right pupil; disks show distinct pallor and visual fields slightly contracted, especially color-field. Knee-jerks present and active. Sensation not disturbed.

*Spinal Fluid.*—Clear; pressure normal; cells 53; globulin +; Wassermann  $\pm$  in 0.3 c.c.,  $\pm$  to + in 0.5 c.c. Patient given nine injections intravenously; also four or five injections of mercury over a period of five months, at the end of which time patient seems in splendid health; disks appear normal; color-fields stationary but show improvement over the original examination. Spinal fluid: clear, pressure normal, cells 15; globulin  $\pm$  to +. Wassermann negative throughout.

CASE 90.—C. P., woman, aged 34, married ten years. (Husband has been under treatment for cerebrospinal syphilis.) Patient unaware of any infection; two months ago began to notice that her eyes were less good; no trouble in the dark, but bright light dazzled her; absolutely no symptoms.

*Physical Examination.*—Pupils react normally, possibly a trifle sluggishly; disks wide; small vessels, narrow; fields markedly contracted; knee-jerks present; right diminished; left active; Achilles jerks present; sensation, heart-shaped area at end of spine diminished to pain.

*Spinal Fluid.*—Clear, pressure normal; cells 120; globulin +; Wassermann + + + in 0.3 c.c. Blood-serum + + +. Patient given intensive treatment with mercury and salvarsan; during seven and one-half months nineteen intravenous and eleven intraspinal injections. There is practically no change in vision. In general health patient feels much better; for the last three or four weeks has had a sensation of numbness; hypersensitive below the knees. Spinal fluid: clear, pressure normal, cells 3, globulin  $\pm$ , Wassermann + in 0.5 c.c.; blood-serum negative.

CASE 26.—O. B. P., man, aged 41, chancre twenty years ago; slight secondaries; no trouble until two years ago, when he noticed blurred vision; has had shooting pains for ten or twelve years down the front of his shins; put on mercury; patient now very nearly blind.

*Physical Examination.*—Pupils mid-wide; react very slightly to light; disks white with bluish tinge; vessels very small and thread-like; reflexes, knee-jerks active; Achilles jerk active.

*Spinal Fluid.*—Clear, pressure slightly increased; cells 133; globulin + +; Wassermann 0.05 c.c. + +; blood-serum + +. Patient treated intensively for four months; fourteen intravenous injections; six intraspinal; after first two or three weeks patient noticed definite growing worse of the vision; recently, however, it has returned to what it was before treatment began. Spinal fluid: clear, pressure normal, cells 8, globulin +; Wassermann 0.1 +. This patient treated entirely with serum salvarsanated *in vitro*.

CASE 44.—E. S., man, aged 52. Chancre twenty-five years ago; very little treatment; slight secondaries; two and one-half years ago double vision; eight



## EFFECT OF INTRAVENOUS AND INTRASPINAL—

Symp-toms	Patient	Case	Pres-sure	Cells	Globu-lin	W. R. Spinal Fluid	W. R. Blood	Clinical Complaint	Physical Examination	Dura-tion of Treat-ment
Pain....	W. A. F.	49	Normal	25	±	0.5 —	—	Pain 2 years., numbness, girdle sensation	Pupils sluggish; K. J. —	9
	J. L. ....	17	Low	37	++	0.3 +++	Not done	3 years pain in arms	A. R. pupils; K. J. ++; sensation disturbed	5
	Dr. L. ...	126	+	52	+	0.1 +++	++	10 years gastric crises, nervousness	A. R. pupils; K. J. —; sensation disturbed	4
	J. P. L.	76	Normal	40	+	0.3 ±	+++	8 years pain, weakness, sl. ataxia	A. R. pupils; K. J. —; rapid heart	5
Pain and Ataxia...	S. H. P.	103	Normal	110	++	0.5 +	—	Pain, ataxia	A. R. pupils; K. J. —; sensation disturbed	11
	S. H. P.	103	Normal	52	—	0.5 ++	—	.....	Pupils unequal; react to light slow	6
	O. T. S.	128	++	22	+	0.3 ++	+	Pain 10 years, ataxia	A. R. pupils; K. J. —; sensation disturbed	5.5
	J. S. ....	93	+	375	+	0.1 +++	Not done	Pain, ataxia 3 years	A. R. pupils; K. J. —; sensation disturbed	12
	J. W. S.	94	Low	131	+	0.3 ++	+++	Pain, ataxia 5 years	A. R. pupils; K. J. —; sensation disturbed	10.5
	J. M. D.	21	++	62	++	0.5 —	+++	Pain, ataxia morphin	A. R. pupils; K. J. —; sensation disturbed	2
	M. D. ...	89	Low	66	+	0.3 ++	—	Pain 7 years, ataxia, morphin	A. R. pupils; K. J. —	3.5
Ataxia...	W. S. P.	95	Normal	51	+	0.5 ++	Not done	Pain 4 months, slight ataxia, irritability	Pupils very sluggish; K. J. —; sensation disturbed	7
	W. A. F.	96	+	133	+++	0.3 +++	+++	Ataxia 2 to 3 months	Pupils equal, regular; react to light and accom.; K. J. —	3
	P. S. P.	124	Normal	62	++	0.1 +++	+++	Ataxia 7 mos.	A. R. pupils; K. J. —	2.5
Optic Atrophy	J. N. W.	91	Normal	53	+	0.3 ± 0.5 ± to +	—	None .....	A. R. pupils; contracted fields; pupils not equal	6.5
	C. P. ...	90	Normal	120	+	0.3 +++	+++	2 months failing vision	Pupils sluggish; fields narrow; sensation disturbed	7.5
	O. B. P.	26	+	133	++	0.5 ++	+++	2 years failing vision	Pupils sluggish; K. J. present; A. J. active	4
	E. S. ....	44	Normal	75	+	0.1 ++	++	2.5 yrs. almost blind, ataxia	Fixed pupils; aortitis; K. J. —	2.5
Bulbar...	H. V. D.	22	+	52	+++	0.3 ++	++	Cyclic vomiting, vagotonia 8 years	Pupils sluggish; heart slow; K. J. +; sensation disturbed	9
Psychic Disturbance....	L. B. K.	18	++	40	++	0.1 +++	+++	Depression, vague fears 3 months	A. R. pupils, not equal K. J. sluggish; sensation disturbed	4
	A. S. B.	12	Normal	25	+	0.1 +++	+++	Mentally sluggish; speech thick and hesitating 1 year	Pupils o. k.; grip not equal; K. J. ++	6.5
	O. R. C.	25	++	327	+++	0.5 +++	+++	Nervousness, vomiting, dizziness 2 weeks	Pupils not equal; reaction slow and stiff; K. J. —	9
	R. F. ...	129	Low	27	++	0.1 +	+	Dulness, depression, wandering 6 years	Pupils nearly equal; reaction to light slow; tremor; K. J. +	2.5
	F. S. C.	24	+	5	±	0.3 +++	—	Dulness, loss of insight; hemiplegia, 8 years	Pupils pin point and A. R.; right, K. J. —; left, K. J. ++	9
	H. H. S.	102	+	34	+	0.1 ++	++	Dulness, wandering speech 6 mos., typical 3 weeks	A. R. pupils; K. J. —; tremor	14
	J. C. H.	66	+	70	±	0.1 ++	0.1 ± 0.2 + ±	Expansion, excitability, delusions 1 wk.	Pupils small, irreg., fixed; K. J. —; tremor	10

\* Fluid had been negative, this after three months without treatment.

## TREATMENTS ON CEREBROSPINAL SYPHILIS

Case	No. Intra-spinous	Pressure	Cells	Globulin	W. R. Spinal Fluid	W. R. Blood	Clinical Complaint	Physical Signs	Time Without Symptoms
	0	Normal	1	— to $\pm$	0.5 —	—	Marked improvement	.....	Nine months.
	9	Low	5	+ to ++	0.5 ++	++	Marked improvement	K. J. less active, no other change.	
	5	Sl. +	0	++	0.5 +++	—	Marked improvement	No change	Severe As. dermatitis.
	5	....	1.2	$\pm$ to +	0.5 + to ++	++	Improved	No change	Sudden increase in ataxia.
	0	Normal	52*	—	0.5 ++	—	Great improvement...	Pupils react to R. and accom.	Two months.
	2	Normal	8	— to $\pm$	0.5 —	—	Great improvement...	Pupils react; K. J. —	Two months.
	6	Normal	...	+	0.3 ++	—	Decline, death.....	No change.	
	8	Normal	2	+	0.5 ++	....	Considerable improvement	No change.	
	3	Low	3	$\pm$ to +	0.5 —	....	Marked improvement	No change.	
	2	+	21	++	Not done	Not done	Very severe pain	No change	Pt. disappeared.
	6	Low	8	.....	0.5 ++ to +++	....	Marked improvement	No change.	
	3	Normal	10	++	0.3 $\pm$ 0.5 +++	—	Slight improvement...	No change.	
	5	Normal	6	++	—	....	Marked improvement	No change	Sudden onset of ataxia.
	4	....	11	+	0.5 +++	....	Considerable improvement	No change.	
	0	....	15	$\pm$ to +	—	....	Marked improvement in fields.		
	11	Normal	3	$\pm$	0.5 +	—	General condition improved	Fields narrow; vision less.	
	6	Normal	8	+	0.1 + 0.3 +++ 0.5 +++ 0.3 ++	....	Stationary, pain started	No change	Slight numbness in calves.
	7	Normal	13	$\pm$ to +	0.3 ++	....	No change.....	No change.	
	12	Normal	10	.....	0.5 $\pm$	—	Entirely well	Practically clear	4 to 5 months without symptoms.
	9	Normal	23	.....	++	0.5 ++	Marked improvement	No change.	
	11	Normal	8	+	0.5 +	....	All clear	Reflexes sl. +...	Slight numbness in feet.
	15	Normal	33	++	0.3 +++	+++	Apparently clear	Pupils react more promptly	Numbness in feet
	5	Normal	32	+++	0.3 + 0.5 +++	....	Marked improvement	No change.	
	18	Low	2	+	0.5 +	—	Mentally active; in- poor; hemi- better	No change.	
	9	+	18	+	0.3 + 0.5 +++	0.2 ++	Entirely clear; at work	Pupils react to light; no other change.	
	8	Normal	5	Omitted	0.5 $\pm$	+++	Entirely clear	No change.	

months ago eyes began to fail; had had four injections of salvarsan; ten injections of mercury; aside from failing vision patient feels well; somewhat unsteady.

*Physical Examination.*—Pupils wide, fixed, irregular, disks bluish white; oval; vessels small, thread-like; patient apparently absolutely blind, although he can distinguish light from dark; dilatation of aorta, double aortic murmur. Blood-pressure, 210; pulse 100 to 140; reflexes, knee-jerks and Achilles jerks absent.

*Spinal Fluid.*—Seventy-five cells; globulin +; Wassermann ++ in 0.1 c.c. Patient given six intravenous and seven intraspinal injections. Spinal fluid: then clear; pressure normal; cells 13; globulin  $\pm$  to +; Wassermann in 0.3 c.c. ++; no change in vision or in any other physical signs.

#### GROUP V: CASE OF VAGUS INVOLVEMENT

The fifth group comprises only one case, which it was thought wise to class by itself because of the striking symptom-complex, depending on the involvement of a single bulbar nerve, the vagus. A startling picture of vagus hypertonia was found; this cleared up temporarily following atropin paralysis of the nerve. It was permanently cured after combined intravenous and intraspinal treatment.

CASE 22.—H. V. D., man, aged 40 years. Severe cyclic vomiting, associated with slow pulse, sinus arrhythmia, sweating and prostration; chancre fourteen years ago; pill treatment; secondaries; stomach trouble in 1906; diplopia on two or three occasions.

*Physical Examination.*—Pupils unequal, irregular, reaction to light stiff; knee-jerks and Achilles jerks very active; sensation, scattered disturbance in touch and pain sensation.

*Spinal Fluid.*—Fifty-two cells; globulin ++; Wassermann ++ in 0.3 c.c. Patient under treatment for nine months; twenty-four intravenous and twelve intraspinal injections. Patient has been absolutely without symptoms for the past three months. Spinal fluid: clear, pressure normal, cells 10, globulin +, Wassermann  $\pm$  in 0.5 c.c.

#### GROUP VI: CASES WITH PSYCHIC DISTURBANCE

The sixth and last group of cases contains instances of psychic disturbance. These varied from confusion, depression and irritability, to expansive ideas, delusions and mania. These cases show remarkable improvement in symptoms, but very slight, if any, improvement in physical signs. There were two types of response in the spinal fluid: the first in which the fluid returned to normal very promptly; the second in which the cell-count came down slowly and the Wassermann rarely disappeared in 0.3 c. c. Clinically, however, no matter what the spinal fluid showed, the cases improved promptly.

CASE 18.—L. M. K., man, aged 42. Chancre twenty years ago; typical secondaries; treated with mercury four or five years; since then perfectly well; three months ago general failure of health, loss of cheerfulness; became nervous and depressed; no headache; no dizzy spells.

*Physical Examination.*—Patient slow in discourse; sometimes loses thread of thought; pupils unequal, irregular, Argyll Robertson; faint tremor of tongue and lips; knee-jerks sluggish; sensation, scattered loss of pain and touch over lower extremities.

*Spinal Fluid.*—Clear; pressure increased; cells 40; globulin ++; Wassermann +++ in 0.1 c.c.; patient treated for four months; received eleven intravenous and nine intraspinal injections. Patient has been treated with serum from another case. He has developed a general dry, itching dermatitis and outcrop of small, slate-colored, pigmented spots from 1 mg. to 2 mg. in diameter; on account of this finding salvarsan has been discontinued. There has been a marked improvement in the patient's symptoms, but he looks bad, pasty and yellow. Spinal fluid: 23 cells, globulin  $\pm$ , Wassermann ++ in 0.5 c.c.

CASE 12.—A. S. B., man, aged 36. Chancre twelve years ago; well treated with mercury; treated almost constantly ever since; nine months ago fell on his head while hunting; though not unconscious was unable to speak; was thought to have a fracture of the base; definite slowness in speech and mental activity.

*Physical Examination.*—Pupils equal and react normally; tendon reflexes very much exaggerated, almost clonus; sensation, diminished pain sense over all, especially lower extremities; memory inaccurate; writing very slow and difficult with a good many mistakes; speech slow, hesitating.

*Spinal Fluid.*—Clear; pressure normal; cells 24; globulin +; Wassermann +++ in 0.1 c.c.; blood-serum +++. Patient under treatment six and one-half months; has had twenty-one intravenous and eleven intraspinal injections. After the first intravenous injection patient vomited, projectile type; pulse-rate was 66. Since then symptoms have cleared up entirely. Knee-jerks diminished, but now speech is practically without hitch; writes as well as ever. Spinal fluid: clear, pressure normal, cells 8, globulin  $\pm$  to +; Wassermann + in 0.5 c.c.

CASE 25.—C. R. C., man, aged 55. Chancre many years ago; treated five years with mercury, never taken well; no signs until a year ago when he had sore mouth; mercury again for six months. Two weeks ago patient fell and struck the back of his head; he was not unconscious; vomited; has been in poor health since; has occasional dizziness, nausea and rapid pulse; marked psychic restlessness.

*Physical Examination.*—Pupils unequal, reaction to light slow and stiff; knee-jerks absent; hearing of left ear slightly impaired; patient has been inclined to be garrulous at times during the past year; sensation not changed.

*Spinal Fluid.*—Clear, pressure increased, cells 327; globulin ++++; Wassermann +++ in 0.05 c.c.; blood-serum +++. Patient has been under treatment nine months; twenty-two intravenous and fifteen intraspinal injections; clinically he is apparently well. Spinal fluid: clear, pressure normal, cells 33, globulin ++; Wassermann +++ in 0.3 c.c. Serological reactions in this case have been extremely stubborn; they have apparently no relation to symptomatology, which has cleared up entirely, save for numbness of feet.

CASE 24.—Dr. F. S. C., man, aged 47. Specific infection at operation eighteen years ago. Eight years ago had a sudden noise in the right ear followed by nausea and vomiting; had slight attack previously; improved after some months and went back to work, but never really normal; three years ago Wassermann +++; given salvarsan several times; during that year weak, with dizziness and vomiting; numbness of left side; complete left hemiplegia and speech disturbance; again given salvarsan; greatly improved; since then had been very depressed; sluggish thought.

*Physical Examination.*—Patient has a rather idiotic expression; speech slow, hesitating; pupils pin-point; Argyll Robertson; remains of hemiplegia noted, including left angle of mouth; weakness of left arm and leg; knee-jerks, left

active; right absent; sensation, no disturbance made out; there is a distinct disturbance of equilibrium.

*Spinal Fluid.*—Five cells; globulin  $\pm$ ; Wassermann +++ in 0.5 c.c. Blood-serum negative. Patient has been under treatment for nine months; thirty-six intravenous and eighteen intraspinal injections. He has improved markedly clinically but still shows definite mental symptoms of the parietic type. He is able to write on the typewriter and walk; is learning to try and help himself. In this respect there has been a very marked change of personality. Spinal fluid shows 2 cells, clear, low pressure, globulin +, Wassermann + in 0.5 c.c.; blood-serum negative.

CASE 112.—H. H. S., man, aged 38. Patient has always been healthy; chancre twenty years ago; received local treatment but no other; no secondaries. Apparently well until six months ago; began to walk crooked; no pain; since then very unsteady; mentally cloudy; very sullen in response; vague, tendency to wander.

*Physical Examination.*—Pupils Argyll Robertson; tongue, lips, tremulous; typical parietic speech; moderate ataxia, writing typically parietic.

*Spinal Fluid.*—Globulin +; Wassermann ++ in 0.1 c.c. Patient given several injections of mercury, followed by twenty intravenous and nine intraspinal injections of salvarsan. Patient's mental state cleared up very strikingly after the first intraspinal injection. From that time on he continued to improve; after a period of two months without treatment patient returned. Spinal fluid: clear, pressure increased 5 cells, Wassermann negative, globulin +. Blood-serum + to ++. Patient shows signs of relapse after interval of three months.

CASE 66.—J. C. H., man, aged 47. Chancre fourteen years ago; treated; no symptoms; apparently well. Suddenly, fourteen months ago, patient began to be garrulous, talking loud; had delusions of exaltation; went into a state of violent insanity; this occurred on the golf links.

*Physical Examination.*—Pupils small, unequal; fixed; fine tremor of tongue and facial muscles; no change in speech; knee-jerks absent; general physical condition good.

*Spinal Fluid.*—Clear, pressure increased; cells 70; globulin  $\pm$ ; Wassermann ++ in 0.1 c.c. Blood-serum  $\pm$  to ++. Patient given twenty intravenous and nine intraspinal injections. After the first two or three treatments patient became more excitable and violent; after that rapidly quieted down; in three months apparently normal. Spinal fluid then showed normal pressure, clear, cells 5, globulin  $\pm$ ; Wassermann negative throughout. Blood-serum +++. Patient has remained well; back at work; he has been without mental symptoms for a year.

CASE 129.—R. F., man, aged 45. Chancre fifteen years ago; mercury treatment; no secondaries except a few buccal patches; treated steadily until the present. Six years ago paralysis of the eye muscles; two years ago Wassermann +++; one year ago nervous breakdown; depression, despair, nervousness. Spinal fluid: 11 cells, Wassermann +++; globulin +; two or three intravenous injections of neosalvarsan; no intraspinal.

*Physical Examination.*—Pupils equal, react to light but very little to accommodation; lips tremulous; reflexes exaggerated to clonus; fine tremor of hands; no disturbed sensation; has apprehension, depression, suspiciousness, alternating with excitability and restlessness.

*Spinal Fluid.*—Twenty-seven cells; fluid clear; pressure low; globulin ++; Wassermann + in 0.1 c.c. Blood-serum 0.1 c.c. +. Under treatment two and one-half months with six intravenous and five intraspinal injections; has been given serum salvarsanated in vitro. After the first intravenous and intraspinal treatment for twelve hours became exalted and quite excitable, very cheerful,



and tremulousness more marked. During the next twenty-four hours slipped back into the depressed state. This has rapidly cleared up. Spinal fluid: at the last examination, clear, pressure normal, cells thirty-two, globulin ++ to ++++, Wassermann + in 0.3 c.c.

An analysis of the cases from a clinical and from a serological point of view indicates that the combined method of treatment produced a marked and prompt improvement in symptoms. There is an equally marked effect on the spinal fluid, but one not necessarily parallel to the clinical improvement. The cell-count often falls rapidly, but the Wassermann and globulin tests yield more slowly in most cases. Just as there seems to be no relationship between clinical symptoms and spinal fluid changes before treatment, so during treatment improvement in the two sets of criteria is irregular and uneven. In this, however, is seen again the indication that the symptoms of cerebrospinal syphilis are dependent on the location of the lesion and not on its character.

#### SUMMARY

Clinically very marked improvement occurs in all groups of cases. In the spinal types pain is usually relieved; ataxia helped in most instances, and not very markedly in a few. The bulbar types and those with fairly pronounced psychic disturbances, depending perhaps on meningeal irritation, show marked improvement in symptoms as well as in spinal fluid. The more definite psychic disturbances also may clear up completely, but their spinal fluids cannot in every case be brought to normal. The cell-count has almost always been reduced in them but the Wassermann test rarely disappears below 0.3 c.c.

In some cases, especially those treated with serum salvarsanized *in vitro*, transient numbness in the feet has appeared; in other cases a slight failing in general robustness which may be an arsenic effect; and in several instances rather severe pains following the intraspinal injection have been seen. In two cases (76 and 96) there has been a sudden increase in ataxia following a period of definite improvement.

Notwithstanding these undesirable features, the improvement in symptoms in almost all cases is of such striking nature that the method should be given a most careful and thorough study by numerous observers. It is, however, a procedure which must be carried out with the greatest attention to the detail of technic in all its steps, otherwise serious symptoms may be induced. At present there is sufficient evidence to show that it is unsafe to give more than two, or at most three, consecutive injections of serum to which salvarsan has been added directly. In no case should more than 0.0005 gm.

be added. On the other hand, apparently any number of intraspinal injections may be given with impunity when serum salvarsanized in vivo is used.

In those cases which do well the rapid and satisfactory improvement may lead to a premature cessation of treatment. For the elaborateness of the procedure arouses an impulse on the part both of patient and physician to curtail the number of treatments. But with our present knowledge of the significance of syphilitic serological reactions, so long as the spinal fluid or blood gives a positive Wassermann test, the case must be looked on as one potentially capable of relapse. Consequently, no matter how well the patient feels and seems to be, treatment must be continued unremittingly until the laboratory tests are persistently negative.

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# THE MECHANISM OF LABYRINTHINE NYSTAGMUS AND ITS MODIFICATIONS BY LESIONS IN THE CEREBELLUM AND CEREBRUM\*

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## AN EXPERIMENTAL INVESTIGATION

Labyrinthine nystagmus both in clinical practice and in discussions of experimental results is designated in accordance with the quick movement. This is an anomaly, since it reduces to a position of secondary importance the most essential factor in the phenomenon — the cause of the deviation of the eyes, from the primary position of equilibrium<sup>1</sup> or from the primary position of the line of fixation of Listing. It must not be forgotten that the eyes of normal subjects have a definite position when at rest or during fixation. Any involuntary departure from this position means that some unusual influence is operative to cause the deviation, and it is precisely this deviation and influence that the clinician is called on to explain. Various influences acting through the central nervous system may cause such deviation of the eyes from the primary position and each one may act in its own peculiar way. The return to the primary position, if at all possible, is likely to be much more uniform than the manner of deviation from the normal. In labyrinthine nystagmus as we have elsewhere described it,<sup>2</sup> the slow component is of labyrinthine origin, and hence is of most significance so far as its relation to the labyrinth is concerned. Variations in the manner of the quick return indicate disturbance in the oculomotor rather than in the labyrinthine or vestibular mechanism. In labyrinthine nystagmus both the slow deviation and quick return are a coordinated series of associated movements, involving contraction of certain groups of muscles and at a certain stage of the process, relaxation of their antagonists, as Bartels<sup>3</sup> experiments demonstrate.

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1. Sherrington: *Integrative Action of the Nervous System*, New York, 1906, p. 279.

2. Wilson and Pike: *Philosophical Trans. Royal Soc.*, 1912, p. 127; also *Proceedings Soc. Exper. Biol. and Med.*, 1913, x, 81.

3. Bartels: *Ueber Regulierung der Augenstellung durch den Ohrapparat*, *Arch. f. Ophth.*, lxxvi, 1; lxxvii, 531; lxxviii, 129; lxxx, 207.

Without lesions in other parts of the central nervous system, there is no double vision at any period. Only when some intracranial complication or oculomotor paralysis exists does double vision arise.

Uththoff<sup>4</sup> distinguishes two varieties of nystagmus: 1. Nystagmus (Bartels', *Pendelnystagmus*), a pendulum movement of the eyes in both directions from the central point of rest. 2. Nystagmus twitching (Bartels' *Rücknystagmus*) when the movement is quicker in one direction. English writers have generally applied the term nystagmus to all oscillations of the eyes without distinction in regard to the variety of the movements. Occasionally the term nystagmus twitching or nystagmoid movement is used to distinguish the more irregular types.

Various mechanisms for nystagmus have been postulated from time to time. Wundt postulated a center for the afferent impulses from the soft parts of the eyes in the cerebellum. As we have shown, however, typical labyrinthine nystagmus may be observed after complete removal of the cerebellum. Bárány has located a nystagmus center in the angular gyrus, and at some point above the oculomotor nuclei, possibly in the pons.<sup>5</sup> Marburg has postulated a nystagmus center in Deiter's nucleus, basing his conclusion on the fact that lesions of Deiter's nucleus, when the rest of the encephalon is supposedly intact, give rise to nystagmus.

Two general objections may be urged against the various hypotheses so far advanced. The first is that writers often assume that, if nystagmus arises from a lesion of a particular region, that region is a center for nystagmus. A lesion of Deiter's nucleus, for example, is merely a lesion of one part of the central portion of the vestibular tract, and nystagmus would naturally arise from such a lesion, just as it does from lesions of the membranous labyrinth of the ear or from intracranial section of the vestibular nerve. The second objection is that little regard has been paid to the whole complex motor mechanism of the eyes, which cannot be described in terms of circumscribed isolated centers, but which must be described in terms of an integrative mechanism or system.

In the consideration of nystagmus after unilateral labyrinthine destruction we are met at the outset with two series of facts. First, nystagmus does not occur in many of the lower vertebrates, but in all of these vertebrate types with movable eyes so far examined, a deviation of the eyes does occur, and this deviation in the lower forms is permanent. Second, nystagmus does occur in the higher vertebrates, but neither nystagmus nor deviation is permanent. In considering,

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4. Uththoff: *Angenerkrankungen bei Erkrankung des Nervensystems*, Graefes-Saemische Handbuch d. ges. Augenh., Section Rückenmark, Part 2, 1904, v, 3.

5. Marburg: *Neurolog. Centralbl.*, 1912, xxxi, 1366.

therefore, the mechanism of nystagmus in the higher vertebrates, we have to explain why neither nystagmus nor deviation of the eyes is permanent in these forms.

In the vertebrates, nystagmus after stimulation or unilateral labyrinthine removal varies as a rule in intensity with the position of the animal in the vertebrate phylum. Its intensity is greatest in the mammals. In *Petromyzon* it is not present, nor does it appear in the frog and the turtle. Some, however, believe that small compensatory movements of the eyes may be observed in the frog. In the cartilaginous fishes it is absent in many forms, e. g., dog-fish. When present, careful observation is required to demonstrate its presence, both in the cartilaginous and in the bony fishes. Ewald<sup>6</sup> showed its presence in pigeons, but so far as our observations go, it is slight and less pronounced than in mammals.

There are definite reasons which lead to the separation of the two phases in nystagmus in regard to cause and source.

1. The deviation alone occurs under an anesthetic. The quick phase only appears as the effect of the anesthetic begins to wear off, and the animal regains consciousness.

2. When the anesthetic is pushed, the slow deviation is one of the last of the phenomena about the head to disappear, and persists nearly or quite as long as the corneal reflex.<sup>2</sup>

3. Bartels has shown that the slow phase alone can be produced by rotation in sleeping children, and that in prematurely born children (7 months) the slow deviation alone can be elicited for some time after birth.

4. We have shown in a previous paper<sup>2</sup> that the quick phase can be eliminated by destruction of the cerebrum and thalamus while the slow persists. As there pointed out, it appears to us that the paths along which the slow deviation occurs are fairly definitely established. We have shown that the slow deviation persists when the animal is at least partly under the influence of a narcotic.<sup>2</sup> Where and how far in their course the vestibular fibers cross the middle line between the labyrinth and oculomotor nuclei has not been established. Loeb's experiments and Bartels' work would seem to indicate a crossing, while the anatomical work of Winkler appears to indicate that the crossing is only partial.

We have endeavored to throw some light on the question by splitting the pons and medulla in the middle line in dogs. So far these experiments tend to substantiate Winkler and our already published hypothesis, since they show that there is no crossing of fibers from the

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6. Bartels: Ueber Regulierung der Augenstellung durch den Ohrapparat, *Arch. f. Ophth.*, 1910, p. 17-21 and p. 51.

vestibular nerve in the anterior two-thirds of the pons and whatever crossing occurs is in the region of the nucleus of the sixth nerve.

Having determined that in labyrinthine nystagmus we are dealing with a double movement in which the slow deviation can be definitely separated by experiment from the return movement, we now look for the source of the quick backward jerk. There are several possibilities of its origin.

We may suppose that the quick backward jerk arises in response to impulses which tend to pull the eye back so that the visual images will fall on a particular retinal field (Wundt). Two series of facts militate against such an hypothesis. Nystagmus occurs in blind subjects when the lesion is in the retina or some part peripheral to the terminations of the optic nerve in the central system<sup>7</sup> when placed on the turning table, or when the ears are irrigated with hot or cold water. And, as we have shown,<sup>2</sup> nystagmus quickly returns when one or both occipital lobes of the cerebrum are removed. Hitzig also noticed nystagmus in blind tabetics.<sup>8</sup>

A second possibility is that the abnormal deviation of the eyes sets up sensory impulses in the afferent endings of the eye muscles themselves, which bring about a return, either reflex or voluntary, of the eyes to the normal position. Nystagmus would then be a response to kinesthetic sensations. We consider this the more probable hypothesis, supported as it is by some observations we have made on third nerve paralysis. It is an hypothesis closely akin to that of Bartels. We have then to trace out the relation of this movement to the cerebrum or thalamus. Bartels' observations on prematurely born children indicate that it involves a path which becomes medullated relatively late.

In comparing the deviation of the eyes which occurs after cortical stimulation with the deviation of the eyes which results from labyrinthine stimulation, it would appear that the relaxation of the antagonistic muscles is not the same in the two cases. Thus from Sherrington's<sup>9</sup> observations it would appear that in cortical stimulation the contraction of a muscle is equal to and balanced by the relaxation of its antagonists. That this is not the case in stimulation of the labyrinth a consideration of Bartels' diagrams<sup>3</sup> appear to show. Here the amount of relaxation in the antagonist falls behind the amount of contraction in the prime mover. As a result we believe that in the deviation of the eyes from labyrinthine stimulation a strain is put on the antagonistic

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7. Mulder: *Arch. f. Ophth.*, 1875, xxi, 68.

8. We hope to show in a later paper that these objections are not so fundamental as sometimes has been supposed. This may be inferred from what is stated in the second last paragraph of this paper.

9. Sherrington: *Integrative Action*, p. 279; *Proc. Royal Soc., London*, 1913, lxxxvi, 225 and 1893, p. 407.



eye-muscles, which strain does not arise in movement from cortical sources. This strain produces a feeling of unusual or uncomfortable position which, when the sensory and motor systems are intact, results in a return to a more comfortable position. The return of the eyes to the median position would on such a hypothesis, be of exactly the same nature as the return of a dog's hind foot from an uncomfortable position when the sensory and motor systems are intact.

We have attempted to locate a region where a lesion consistently affects or abolishes the quick component of nystagmus arising either as a result of destruction or stimulation of the labyrinth. We have pointed out in a previous paper that such a region does not exist in the cerebellum. As there shown, the removal of the lateral lobe or of the vermis or of the whole cerebellum may affect, but does not abolish, the nystagmus which follows labyrinthine destruction. Since these results were published, we have repeated in detail these experiments and with the same result. Accordingly, we feel justified in saying that neither the slow deviation nor the quick return has any necessary pathway nor any indispensable center in the cerebellum.

We have previously pointed out that, in cats and dogs, complete decerebration, including the corpora striata and the thalamus, wholly abolishes the quick component after labyrinthine stimulation or removal, although the slow deviation of the eyes persists. We are unable to confirm Bauer and Leidler<sup>10</sup> who report the occurrence of nystagmus after removal of all parts of the cerebrum as far down as the corpora quadrigemina. A number of new experiments substantiate our former conclusions. The quick movement in nystagmus arises from some mechanism above the corpora quadrigemina—a point in which we confirm Bartels' view. The question becomes, then, whether the quick component of nystagmus arises from the thalamus or from the cerebrum. Anatomically, afferent tracts pass from the eye-muscles back to the oculomotor nuclei, and then, in all probability, through the thalamus where they are relayed, and then on up to the cerebral cortex. Efferent tracts arise in at least three different regions of the cerebral cortex and pass down to the oculomotor nuclei. It appears to us that the mechanism of nystagmus involves cortical cells and areas, and that any return of nystagmus after injury to a part of the cortical mechanism may be explained by supposing that the shorter, more primitive paths through the subcortical regions become passable for nervous impulses.

In assuming that the mechanism of nystagmus involves thalamic paths and nuclei alone, we meet with certain difficulties in arriving at a satisfactory explanation. We must explain why, when every other part

10. Bauer and Leidler: *Arbeit. a. d. Wien. Neurol. Institut.*, 1911, xix, 155.

of the efferent oculomotor path is open, as shown by the presence of the corneal reflex, and the slow deviation of the eyes in response to labyrinthine stimulation, the path involved in the production of the quick movement should be the only one to be blocked. The explanation of shock does not explain anything until we tell what shock is. A hypothetical principle of explanation which in the last four decades of investigation, has proved so confused and conflicting, as shock, and which follows no laws so far discovered, and apparently, no discoverable laws, is not likely to lead us far as a constructive principle. We may point out that shock if present at all, follows the same general course with reference to nystagmus that it follows in the case of the skeletal muscles generally; that is, it is exerted on the afferent pathway, since, to all our tests, the efferent path is so obviously open.<sup>11</sup>

We may assume, then, as a working hypothesis, that some cerebral mechanism is involved in the production of the quick phase of nystagmus, and it remains to trace out as far as possible the regions and tracts concerned. There are two possibilities: 1. Both cerebral hemispheres may be involved in the production of the quick phase of nystagmus when the slow component is in a given direction. 2. Only one cerebral hemisphere may be involved. If only one is involved, what relation does it bear to the direction of the slow or labyrinthine phase? Experiment shows that the second possibility is more nearly the true one so far as the lateral movement is concerned. Space does not permit the recital of the details of the experiments at this time, and a brief presentation must suffice. This conclusion is based on the following:

1. The results of removal of one labyrinth and one cerebral hemisphere, noting the presence or absence of nystagmus.
2. The results of electrical, caloric and rotation tests in such animals.
3. The results of electrical, caloric and rotation tests in animals in which both labyrinths are intact, but in which one cerebral hemisphere had been removed.

As a general result, we may state that complete removal of the cerebral hemisphere on the side of the slow deviation abolishes all except a small rotatory component of the quick phase of nystagmus. Complete removal of the cerebral hemisphere of the side toward which the quick component is directed has but little effect on the quick movement.

Rotation, electrical and caloric tests on such animals again show the dropping out of the quick phase of nystagmus when the slow deviation of the eyes is directed toward the side of the cerebral lesion, and

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11. Pike: *Am. Jour. Physiol.*, 1909, xxiv, 124.

little or no effect when the slow component is directed toward the uninjured side of the cerebrum.

We may here note in passing that injury to the anterior corpus quadrigeminum of the side to which the slow deviation of the eyes is directed does not abolish the nystagmus, either in its slow or quick phase, but it does bring about a dissociation of the eye movements.

These tests, when repeated on animals with both labyrinths intact, but with removal of one cerebral hemisphere, lead to the same conclusion.

We have attempted in cats, dogs and monkeys to find some region in a hemisphere where a lesion will modify or abolish the nystagmus which follows stimulation or destruction of the labyrinth. In the course of the experiments we have removed the various areas of the cortex, frontal, parietal, occipital and temporal, and have also at times destroyed the subcortical ganglionic masses. Having destroyed these areas, we have then stimulated one or both labyrinths with the electrical current, with hot and with cold water and by rotation. We have also in many of these cases destroyed one labyrinth either concomitantly with or subsequent to the cerebral lesion—a labyrinth either on the side of or opposite to the cerebral lesion. We cannot at this time enter into the details of the results, which will be published in full later, but we desire to state here that the only region where we obtain consistent alteration of the labyrinthine stimulation, and that only so far as the quick component is concerned, is the region of, or adjacent to, the temporal lobe. In these cases we found that stimulation of the labyrinth on the side opposite the cerebral lesion with cold water or with the anode gave typical labyrinthine nystagmus, lateral in character, while stimulation with hot water or the cathode gave deviation, but no lateral nystagmus. We also found that destruction of the labyrinth on the side of the cerebral lesion gave no nystagmus. There was further noted in some of our cases that the eye on the side of the lesion showed a rotatory movement around an anteroposterior axis, while this movement was wanting in the eye of the opposite side.

To sum up, our idea of the mechanism of nystagmus is first, an agency somewhere which produces a deviation of the eyes from the primary position of equilibrium or the primary position of the line of fixation of Listing. In labyrinthine nystagmus, this agency lies in the labyrinth. The internal rectus muscle on the side of the slow deviation and the external rectus on the opposite side are subjected to a strain greater than usual. This strain, resulting in the stimulation of the sensory or afferent endings of the eye-muscles, sets up afferent impulses which are conveyed to the cerebrum over the afferent fibers

in the third, fourth and sixth cranial nerves.<sup>12</sup> These afferent impulses in their turn set up efferent impulses in the oculomotor cells of the cerebrum, which result in a quick, jerky contraction of the internal rectus on the side of the slow deviation and of the external rectus of the opposite side, with relaxation of the antagonistic muscles. The effect is a restoration of the eyes to the primary position. The eyes do not go beyond this median position when the cerebrum is intact, since the afferent impulses to contraction of the external and internal rectus muscles concerned cease when the eyes reach this position of equilibrium.

Lesions of the cerebral hemisphere on the side of the slow deviation of the eyes abolish or reduce the quick component, since it is from the hemisphere of this side that the efferent impulses concerned in the pulling of the eyes back to the median line arise.

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12. Tozer and Sherrington: Receptors and Afferents in Third, Fourth and Sixth Cranial Nerves, *Proc. Royal Soc.*, 1910, p. 450.

# THE RELATION OF PANCREATIC ORGANOTHERAPY TO KETOGENESIS \*

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## I. INTRODUCTION

The earlier trials, both laboratory and clinical, of pancreatic opotherapy, were conceived and undertaken at a time when the ground-problems of diabetes — almost coextensive as they are with the whole domain of pathometabolism — were not so clearly defined as at present. Nevertheless, on historical consideration of these attempts it becomes obvious that the propelling forces behind them all were, first, the urgent demand for a successful therapy, and, following that, the vague assumption, dating from or even antedating von Mering and Minkowski's classic work, that the pathogenetic basis of the clinical entity diabetes is the absence or deficiency of a pancreatic hormone or internal secretion necessary in some sense to carbohydrate utilization. Whether this basal assumption of an internal secretion shall prove valid or not, it is certain that the attempts at pancreatic organotherapy have amply justified themselves, not as yet by realizing much of practical value to the clinician, but by virtue of the increasing light they have thrown on the problems of general and of diabetic metabolism.

The earlier workers in this domain contented themselves largely with the investigation of the effects of various types of opotherapy on the most obvious symptom of diabetes, namely, *glycosuria*. Only recently has the work — or some of it — become more critical in the sense of adopting more fundamental criteria, such as the effect on glycemia and on the respiratory quotient.

Here, as in all such problems, it has taken much continued effort to eliminate irrelevant, interfering factors, which have vitiated results and invalidated researches; for example, many of the pancreatic extracts used have been of an acid reaction, regardless of the fact that this physical condition, per se, influences greatly the state of hepatic glycogen, and hence the glycosuria. Again, many investigators have selected one type of opotherapy (as injections or transfusions) to the exclusion of other types, and apparently at random, that is, without due consideration of the reasons for so choosing.

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Correlating the many researches, however, the influence of pancreatic opotherapy on *carbohydrate metabolism* has, at least in some of its aspects, been rather minutely investigated. In contrast, there are in the literature only casual references to the influence of organotherapy on the formation and excretion of *ketone bodies*, and it has been the intent of the present work to investigate this relation more precisely.

As it is particularly in the complex field of diabetes that progress has been so hampered and retarded by preconceived theories, it seemed best to attack each segment of the problem unprejudiced by any general, hypothetical concepts. Hence, all unproved assumptions as to an internal pancreatic secretion, its nature, or even its existence have been insistently avoided. Also a neutral ground as to the importance of the ketone bodies for the clinical picture of diabetes has been assumed. There is at present no certainty as to whether "acidosis" is a complication of diabetes, or an integral part of the deranged functioning, as to whether the ketones are the cause of coma diabeticum or merely harmless by-products of the essential vicious metabolism. Accordingly, in the introductory bibliographic interpretation given below I have sought to eliminate all unproved dogmas, and to keep within the bounds of objective data.

## II. HISTORICAL AND CRITICAL

Any investigation of the influence of pancreatic organotherapy on ketogenesis must obviously take into account, at every step, the allied problem of the effect of such opotherapy on glycosuria and on the general constitutional condition; this because of the close relationship subsisting between carbohydrate metabolism and "acidosis." I shall accordingly, in conformity with the following schema, briefly review the past work along each of these lines:

1. Effect of pancreatic opotherapy on glycosuria and the general condition.

- (a) Feeding.
- (b) Injections.
- (c) Transfusions and parabioses.
- (d) Grafts and transplants.

2. Effect on ketoplasia and ketogenesis.

### EFFECT OF PANCREATIC OPOTHERAPY ON GLYCOSURIA AND THE GENERAL CONDITION

#### (a) *Feeding of Gland and Its Extracts and Ferments*

When dogs suffering from chronic, pancreatic diabetes are fed with raw pancreas, the glycosuria increases three- or four-fold; cooked



gland gives negative results.<sup>1</sup> The feeding of raw muscle and other tissue extracts exerts a similar augmentative effect on the glycosuria.<sup>2</sup>

Fresh pancreas (of sheep, calf or fish) in human diabetes has given either negative results, sometimes accompanied by slight subjective (psychic) improvement,<sup>3</sup> or else an actual increase of glycosuria.<sup>4</sup> The feeding of pancreatin also causes greatly increased glycosuria.<sup>5</sup>

Positive results are few and questionable. Ausset<sup>6</sup> claimed lowering of glycosuria and even complete "cessation of diabetes" in diabetic dogs and man fed on cooked pancreas. In one group of cases, however, namely, the diabetides of distinctly pancreatic type with deficient fat and protein absorption, there seems to be abundant evidence of improvement in absorption and general nutrition following exhibition of pankreon,<sup>7</sup> or of raw sheep pancreas.<sup>8</sup>

As to the influence on carbohydrate tolerance in this group of cases, Wegele and Meyer claimed an improvement, while Mosenthal in his carefully controlled observations denies any effect. Pratt, Spooner and Murphy<sup>9</sup> induced in dogs the chronic diabetes of slowly progressive pancreatic atrophy, with lowering of dextrose tolerance and markedly decreased absorption of fats and proteins. Raw sheep pancreas was then administered over prolonged periods. In general, fat and protein absorption were improved, and in one animal the carbohydrate tolerance was greatly increased. Even in this case, however, the tolerance could not always be raised; moreover, in other dogs this influence was slight and in a late case<sup>9</sup> negligible.

With regard to the treatment of diabetes by feeding acid extracts of duodenal mucosa or secretin, a few authors<sup>11</sup> have claimed improvement, but most observers report negative results.<sup>12</sup> Altogether the destructive criticism of Pflüger<sup>13</sup> and Leschke,<sup>14</sup> which showed most such results to be the expression of fluctuations common to all non-total diabetics, seems to be applicable also to the later results, but with the exception noted above — namely, the positive influence on digestion and assimilation in *pancreatic* diabetes. Moreover, lessened glycosuria when observed is almost certainly due at times to a toxic lessening of renal permeability, the hyperglycemia not being decreased (see below).

#### (b) Injections of Pancreatic Extracts and Ferments

*Intraperitoneal* injections of emulsions of fresh pancreas in depancreatized dogs sometimes cause marked drops in glycosuria.<sup>15</sup> But all such effects are due to a peritoneal irritation with reflex *decrease of renal permeability*.<sup>16</sup> No improvement results in human diabetes from intraperitoneal injection of emulsions.<sup>17</sup> Repeated large doses given to guinea-pigs and depancreatized frogs by the peritoneal and also by the combined subcutaneous and peritoneal routes not only result in no

improvement of the diabetes, but are actually very toxic and uniformly increase glycosuria. Extracts inactivated by heat give negative results.<sup>14</sup>

*Subcutaneous* injections of pancreas may cause marked drops of glycosuria in human diabetes,<sup>18</sup> and in the pancreatic diabetes of dogs.<sup>19</sup> Certain pancreatic extracts given subcutaneously cause diminished glycosuria in the epinephrin — and phloridzin — diabetes of animals.<sup>20</sup> But such reductions of glycosuria are always associated with general, constitutional depression or with decreased renal permeability,<sup>21</sup> the latter accompanied by increase of blood-sugar.<sup>22</sup> There is also abundant evidence that diabetes is not ameliorated in any of its aspects. Thus, subcutaneous injections of extracts give negative results in human diabetes.<sup>23</sup> In depancreatized dogs they give similarly negative results,<sup>24</sup> and even cause a toxic increase of glycosuria.<sup>25</sup> Leschke<sup>14</sup> verified this for guinea-pigs and depancreatized frogs. Indeed, subcutaneous injections of extracts of almost any organ cause toxic effects and a glycosuria (liver, spleen, heart, kidneys, pancreas, skeletal muscle<sup>26</sup>).

*Intravenous* injections also give therapeutically disappointing results. Thus, Williamson<sup>17</sup> observed no influence over human diabetes, and Hédon,<sup>27</sup> working on diabetic dogs, observed no improvement, while his tables actually show a glycosuric effect. Zuelzer<sup>28</sup> administered his "hormone" of dog pancreas intravenously to depancreatized dogs and human diabetics. The resulting temporary decreases in glycosuria and ketonuria are admittedly secondary to the marked constitutional (toxic) depression.<sup>29</sup> Alcoholic extracts administered intravenously give negative results; aqueous extracts cause transient lowering of glycosuria and dextrose-nitrogen ratio, but this is interpreted as a toxic depressor action rather than as specific regulatory.<sup>30</sup>

It seemed at first that extracorporeal perfusions, while not strictly opotherapeutic, might throw light on the problem. Thus, the addition of pancreatic extracts to blood perfused through the beating heart caused a marked disappearance of dextrose, which was thought to be due to the "pancreatic hormone."<sup>31</sup> This view is now abandoned.<sup>32</sup> The sugar disappears not through oxidation, but by polymerization.<sup>33</sup> Other fallacies are also inherent in the perfusion methods as applied to pancreatic opotherapy.<sup>34</sup> Thus slight changes in reaction affect the storing of glycogen,<sup>35</sup> also slight changes in the concentration of K-ions influence the disappearance of sugar from the blood.<sup>36</sup> When pancreatic extracts are added to the blood perfused through isolated surviving livers, there does not appear to result any increased deposit of glycogen or any diminished glucose production.<sup>37</sup>

Two recent researches are of especial importance because based on the realization that fluctuations in glycosuria are of manifold significance, owing to the complexity of the factors which may influence them and that the final test of a "hormone" will be the restoration of pancreatic function to the entire organism, the best criterion being conceived to be the respiratory quotient. Thus<sup>38</sup> pancreatic extracts given intravenously and subcutaneously to depancreatized dogs exert no influence on the respiratory quotient. After large injections there is sometimes a temporary fall of glycosuria due to decreased renal permeability, but soon followed by a compensatory rise.

Feeding or injections of *diastase* probably have no relation to pancreatic opotherapy, since it is not a function of the pancreas to deliver diastatic ferment to the blood.<sup>39</sup> Moreover, the lowered glycosuria sometimes following intravenous injection of diastase<sup>40</sup> is certainly secondary to the general systemic depression.<sup>14</sup>

According to some observers there results an actual increase of glycosuria on intravenous or subcutaneous injections of diastase,<sup>41</sup> or of pancreatic juice.<sup>42</sup>

### (c) *Transfusions and Vascular Parabioses*

When pancreatized dogs receive transfusions of fresh blood from normal dogs their glycosuria is sometimes uninfluenced,<sup>43</sup> but more often is temporarily decreased.<sup>44</sup> Fresh, defibrinated blood gives the same result.<sup>45</sup> The hyperglycemia is not reduced.<sup>46</sup>

Similar results follow the crossing of circulation between normal and diabetic dogs by vascular parabioses. This is true no matter what vessels are anastomosed, but the reduction of glycosuria is greatest when the blood passes from the pancreatic circulation of the normal into the systemic circulation of the diabetic dog.<sup>47</sup> However, this reduction of glycosuria has no relation to specific opotherapy. It is due to a temporary, toxic decrease of renal permeability, as Hédon himself admits in his last papers.<sup>48</sup> It is associated with oliguria and albuminuria, and with general constitutional disturbances—fever, anorexia and marked depression. The hyperglycemia is either increased (normal dog) or not reduced (diabetic dog). Moreover, a few hours after such transfusion there occurs a compensatory rise in dextrosuria, balancing the temporary reduction.<sup>49</sup>

The introduction of foreign bloods and serums per se is partially responsible for these toxic phenomena. Thus in Hédon's experiments the normal dog became immediately glycosuric and hyperglycemic, and when two totally diabetic dogs were joined both developed oliguria and reduction of glycosuria, and both invariably died. Pancreatic extracts have been repeatedly shown to decrease renal permeability to

dextrose,<sup>50</sup> but Hédén's last experiments make it probable that the toxic effect on renal permeability is due to the foreign serums.

When the more fundamental criterion of respiratory quotient is invoked, it is found that the transfusion of large amounts of fresh, defibrinated blood, or whole blood, from normal to diabetic dog gives rise to no change in the respiratory quotient, and presumably no increase in the oxidative capacity of the organism. Crossed circulations are also negative in the same sense.<sup>55</sup> A similar toxicity of transfusions for the *human* diabetic is strikingly shown by the case of Raulston and Woodyatt,<sup>51</sup> who directly transfused blood from a normal man to his diabetic brother. The diet and metabolic data had been carefully controlled for months. The result was a marked (late) increase in dextrosuria, and in ketonuria. There was no evidence of improved carbohydrate utilization, and the authors believe blood transfusions to be definitely contra-indicated in severe diabetes.

With reference to the use of lymph Biedl, after reviewing the literature,<sup>52</sup> concludes on the basis of original experiments that intravenous and subcutaneous injections tend to lower the dextrose-nitrogen ratio.

#### (d) Grafts and Transplants

The extirpation of all the pancreas except a small lobe of the processus uncinatus, with subcutaneous implantation of the latter,<sup>53</sup> its vascular pedicle being preserved, is generally referred to as a "transplantation,"<sup>54</sup> but is rather an incomplete pancreatectomy with dislocation of the remaining fragment. Rarely such a lobe lives and functionates after cutting of the vascular pedicle, through establishment of secondary vascularization from the local tissues.<sup>55</sup> This amounts to an autotransplant, but is equivalent, from the point of view of organotherapy, merely to any incomplete pancreatectomy.

Many attempts at heterotransplantation and homotransplantation have failed.<sup>56</sup> Carrel,<sup>57</sup> in his latest address, shows on general grounds that *autotransplants* of organs are often viable, *homotransplants* or *heterotransplants* practically never.

Autotransplants of part of the pancreas into the spleen, the rest of the pancreas being extirpated, have succeeded, as shown by their ability to prevent the total diabetes. These have been *free*<sup>58</sup> or pedicled with subsequent severing of the vascular stalk.<sup>59</sup> The undoubtedly successful functioning of such autotransplants without pedicle teaches us no more than Lombroso's original experiment.

These procedures seem directly comparable with the extirpation of the hypophysis and immediate reimplantation into the cerebral cortex, with prolongation of life and viability of the graft for over a month.

In this case, too, the *glandular deficiency* is established; otherwise the autotransplant will probably not take.<sup>60</sup>

Forschbach<sup>61</sup> united dogs parabiotically, bringing peritoneal cavities and homologous layers of the parietes into continuity. There was *no vascular* continuity, and hence this procedure is the equivalent, not of transfusion or of crossed circulation, but of transplantation. On extirpation of the pancreas of one, the ensuing glycosuria was slight and developed late. The normal dog developed a (toxic) glycosuria. The wounds healed well and no diabetic cachexia developed. When the animals were separated, the depancreatized dog soon died of infection or cachexia.

If the pancreas of a pregnant dog near term be removed no glycosuria develops; after delivery it becomes intense at once.<sup>62</sup> Are these last two observations to be explained on the basis of internal secretion or of toxic effects on renal activity?

### Summary

To summarize with reference to the effect on glycosuria, the general constitutional condition, and the carbohydrate oxidative power of the organism:

1. *Feeding* of fresh pancreas has usually been observed, both clinically and experimentally, either to have no effect on, or else actually to increase the glycosuria. This action is hardly specific for pancreas, being induced by many raw tissues. It is doubtful whether carbohydrate tolerance has ever been increased. Good effects as to increased absorption of fats and proteins and improvement of nutrition must be conceded. Unfortunately, glycosuria has been made, in all feeding experiments, almost the sole criterion of the influence on carbohydrate utilization.

2. When, after *injections* of extracts and emulsions, lessened glycosuria occurs, it is referable to general systemic depression or to decreased renal permeability. Intraperitoneal injections are absolutely fallacious, because of the renal reflex. Under many conditions there is even a markedly increased toxic glycosuria. Adjudged by the most reliable criterion (respiratory quotient) the effects on carbohydrate intermediate metabolism are nil.

Injections of enzymes (diastases) also cause a toxic increase of glycosuria, but sometimes a temporary decrease of glycosuria associated with systemic depression.

3. *Transfusions* and *crossed circulations* always have a toxic action. Sometimes the glycosuria is temporarily reduced, in which case there are either associated symptoms of general depression, or else evidence of reduced renal function (albuminuria, oliguria, later compensatory

rise of glycosuria). Sometimes there is a toxic increase of glycosuria, of ketonuria, and of toxic products of protein catabolism. Hyperglycemia is not decreased. There is no rise in the respiratory quotient. The reaction is bad in every sense as to the general systemic effect.

4. The successful (auto-) *transplants* show merely what was known from Lombroso's original experiment, namely, that if a living, functioning fragment of the animal's own pancreas of sufficient size be present in the blood circuit, diabetic symptoms will be inhibited.

The parabioses (Forschbach) and the pregnancy experiments (Carlson) seem to be the equivalents, from the opotherapeutic point of view, of *homotransplants*. In each case there was established a pancreatic insufficiency of one animal, and an attempt to remedy this by supplying the products of the pancreas of another individual of the same species. It is noteworthy that in only these two of many researches was an opportunity afforded, by virtue of the absence of vascular continuity,<sup>63</sup> for intimate interchange (parallel to osmosis of crystalloids), without an actual mixing of foreign bloods or serums. And in these two researches we possibly have some evidence of the influence of a pancreatic hormone over the fundamental causative processes of diabetes. In Forschbach's experiments the reparative functions of the diabetic animal were good, which is much more significant than any reduction of glycosuria. Even here there is the possibility of a toxic reduction of glycosuria.

#### *Factors Influencing the Degree of Glycosuria*

It is evident that the *degree* of *glycosuria* observed in any given opotherapeutic experiment is a *resultant* of *several* opposing factors, some tending to increase, others to decrease it, and probably none to be interpreted as really therapeutic in the sense of exerting any curative influence on the underlying metabolic error of diabetes. Some are more in evidence on parenteral, others on enteral administration. It is possible to designate roughly some of these factors:

##### A. Lessening glycosuria.

(a) Toxic decrease of renal permeability.<sup>64</sup>

(b) Decrease of glycosuria associated with general constitutional depression (as obviously in Zuelzer's hormone work), comparable to the decrease of glycosuria and ketonuria observed in moribund diabetics.

(c) It has been definitely shown that acidity or alkalinity of the extract per se may exert a marked effect on glycosuria and on glycemia, through its influence on the state of hepatic glycogen. Administration of even dilute acids mobilizes hepatic glycogen, alkalies exerting the reverse effect.<sup>65</sup>



## B. Increasing glycosuria.

(a) The opinion has very generally been held that the increased glycosuria observed on *feeding* of pancreas may be due to *bettered absorption*, especially of carbohydrates.<sup>66</sup> That other factors are at work is shown by the fact (Sandmeyer) that even after decrease of daily rations of diabetic dogs by 50 per cent., the glycosuria increases on pancreatic feeding from three to tenfold.

(b') There is certainly a *toxic glycosuria*, or perhaps several types. And it is sometimes, if not always, accompanied by hyperglycemia. Even the increased glycosuria of pancreatic *feeding* has been interpreted by some as toxic, rather than due to increased absorption,<sup>67</sup> Reach having proved that it is not due to better digestion or assimilation. The toxic split products of proteins are held to be the responsible agents, and this seems probable, inasmuch as the feeding of various amino-acids to diabetic dogs (both depancreatized and phloridzinized) and human diabetics results in a toxic increase of glycosuria.<sup>68</sup> The increased glycosuria of *parenteral* opotherapy is almost certainly toxic. Leschke<sup>14</sup> believes enzymes (for instance, trypsin) to be the agent, but hints at the possibility of non-catalytic (chemical) toxins.<sup>69</sup> It is possible that the glycosuria and the toxic (or lethal) phenomena have different agents.

As to the point of attack of such a glycosuric toxin, one can at present only speculate as to whether the action is through increased hepatic glycogenolysis (mobilization of glycogen), toxic lowering of the general tissue oxidative capacity, increased renal permeability, or some other mechanism.

After repeated large injections of gland extracts (pancreas, thyroid, liver, kidneys, etc.), there develop no micropathologic changes *specific* for the various extracts, but in all cases, parenchymatous degenerative hepatitis and nephritis with perivascular infiltrations, hyperplastic follicular splenitis and hyperplasia of lymph-nodes.<sup>70</sup>

(c') Finally, as a possible explanation of increased glycosuria, Cohnheim and Klein† note that the foods causing the greatest flow of pancreatic juice (raw meats) are the ones causing glycosuria. They suggest that the internal and external pancreatic secretions are likely to vary inversely as to their potency, and that hence the increase in external secretion will be correlated with a decrease in internal secretion, even to the point of producing glycosuria. Of course, this is speculative.

Historically it will be noted that really positive results of opotherapy have receded as the criteria have become more exacting. Attention was earlier focused on the glycosuria, and to a lesser extent

†. Cohnheim and Klee: Ztschr. f. physiol. Chem., 1912, lxxviii. 464.

on the general clinical condition. Of late more stress is being given to the true indices of carbohydrate oxidative power, and in the near future even heavier demands will be made on any attempt to establish the claims of an opotherapy, in conformity with the growing tendency to discard the assumption that the disturbances of carbohydrate intermediary metabolism constitute the sole essence of the entity diabetes.<sup>71</sup>

#### INFLUENCE OF PANCREATIC OPOTHERAPY ON KETOGENESIS

Only a few isolated and conflicting observations are recorded in the literature. Salomon<sup>72</sup> observed an increase of acetonuria after the use of pancreon in a case of pancreatic diabetes.

Sandmeyer<sup>73</sup> observed in his chronic diabetic dogs that the feeding of *raw* pancreas caused increase of glycosuria (see above) with appearance of acetone and diacetic acid. The latter was noted twice,<sup>74</sup> and *only* on administration of raw pancreas. No quantitative determinations were made.

Zuelzer,<sup>28</sup> using the hormone referred to above, in depancreatized dogs and moderately severe human diabetes, observed lessened "acidosis," as indicated by the color intensity of qualitative tests of urine. But Forschbach<sup>75</sup> invalidates these conclusions just as he had their deductions as to decreased glycosuria (see above), on the ground of the general toxic depression. Moreover, he observed *no decrease* of ketonuria, even with the marked constitutional reaction.

Mosenthal,<sup>76</sup> in a single case of human diabetes, probably of pancreatic type (displaying deficient fat and protein absorption, with large fatty stools and undigested meat fibers), found that on a regimen of raw sheep pancreas feeding, the urinary ammonia was greatly increased, for example, from about 2.2 gm. on ordinary diet to about 5.2 gm. after exhibition of pancreas, this rise being associated with a corresponding increase in ketonuria, the beta-oxybutyric acid rising from 2.2 gm. to 32.1 gm. Mosenthal's observations were clinical, and in a particularly severe case,<sup>77</sup> it became necessary, on considerations of safety, to interfere with the experiment in such ways as to detract from the clear-cutness of the interpretation. Thus, the use of opotherapy had to be frequently interrupted; alkalies were administered from time to time; also there is some ambiguity as to the amounts of fat fed, and the influence of other food elements. This is not mentioned in a spirit of criticism, as the duty to the patient obviously had to take precedence of the research. The great interest in Mosenthal's report lies in the fact that the feeding of raw pancreas gave rise to tremendous ketonuria in a case of undoubted "pancreatic diabetes." Under the opotherapy there was, except for the (at times alarming) increase of ketogenesis, a marked general improvement, and certainly increased utilization of fats; thus "the stools changed from those

typical of pancreatic disease to what appeared to be normal movements." He concludes that the increased ketogenesis is due to increased intestinal absorption of fats. He evidently believes (following most authors) that dogs totally pancreatic-diabetic excrete no ketones, and explains this on the basis of non-absorption of fat. This question is examined below.

Raulston and Woodyatt,<sup>51</sup> in their clinical research described above, noted, on direct transfusion of blood from normal to diabetic man, a marked increase of ketonuria. The total beta-hydroxybutyric acid increased from 190 gm. for the five days preceding, to 273 gm. for the five days following. Their metabolic work seems perfectly controlled as to diet and other factors. Dakin and Dudley<sup>78</sup> perfused dogs' liver with blood containing added substances, known from Embden's experiments to yield aceto-acetic acid freely under these conditions, as tyrosin, the sodic salts of butyric and homogentisinic acid. To this perfusing blood were then added fresh extracts of pancreas, or heated pancreatic extract of skeletal-muscle extract, all prepared by grinding the fresh tissues in water. No decrease in hepatic ketogenesis resulted. Their conclusion is that they have found no evidence that the pancreas furnishes an enzyme or hormone, the absence of which leads to acidosis in the diabetic animal.

### III. METHODS

#### A. CHOICE OF ANIMALS; ACIDOSIS IN DOGS

In undertaking a research on "acidosis" the selection of an animal is a matter of great importance. In general diabetic work, the dog has been, of course, at once the most available and most useful. But where any consideration of ketogenesis is concerned, one must raise the question as to whether a carnivore is suitable, the opinion being somewhat widespread that there is some fundamental difference in the reaction of dogs and man to factors of ketone formation; there has been a good deal of skepticism as to whether "acidosis" is of the same nature in dogs, or, indeed, even as to its occurrence. If such doubts be well grounded, much experimental work will have to be revised.

Minkowski<sup>79</sup> found that ketonuria does not *always* follow total pancreatectomy in dogs, and hence interpreted ketonuria as a complication of diabetes. Brugsch and Bamberg<sup>80</sup> held that "acidosis" furnishes the essential difference between canine and human diabetes, extreme acidosis never occurring in depancreatized dogs, which invariably die of inanition rather than in coma. They attach great importance to this postulate, believing that a severe diabetes with pronounced acidosis is probably not a pancreatic diabetes.

Allard<sup>81</sup> and Minkowski<sup>82</sup> opposed this view, proving that in dogs totally depancreatized, acidosis is not rare. Five of Minkowski's dogs

excreted large amounts of ketone bodies. Allard cites three cases of marked acetone excretion (from 2 to 3 gm. total acetone in dogs of 8 to 9 kg.), moderate amounts of acetone, diacetic and beta-oxybutyric acid being demonstrated in many depancreatized dogs. Normal adult dogs on starvation show only traces. Both Allard and Minkowski describe cases of probable death in coma. This ketonuria of dogs has been abundantly confirmed.<sup>83</sup> It is constant after total pancreatectomy.<sup>84</sup>

Large amounts of diacetic acid are formed in the surviving livers of depancreatized dogs, perfused with blood.<sup>85</sup>

On the basis of all these findings and of my own observations, I certainly disagree with Allen<sup>86</sup> in his conclusion that "totally depancreatized dogs are generally free from ketonuria." I can affirm absolutely on the basis of my own experiments that *totally* depancreatized dogs *always* develop ketonuria. I can, however, confirm Allen's statement that they often give no ferric chlorid reaction when excreting large amounts of acetone. However, I have at some time or other in every such dog always found aceto-acetic acid by certain of the tests.<sup>87</sup>

With regard to the factors influencing ketonuria in dogs, it occurs in *chronic* diabetes (Sandmeyer<sup>73</sup>) as well as in the total type. It is also generally held that in dogs, ketonuria is *not* increased in starvation, but rather reduced; also is not lessened by utilization of carbohydrates; is augmented by excessive meat feeding, and hence runs parallel to nitrogen excretion.<sup>88</sup>

These statements are in general true for adult dogs, but one should not conclude that dogs would hence be unsuitable for "acidosis" work. It is certain that in dogs, as in man, a lowered carbohydrate intermediate metabolism predisposes to acidosis. Marum's<sup>89</sup> observation that in phloridzin diabetes of dogs acidosis occurs only after exhaustion of the glycogen stores proves this. While dextrose-feeding has but little influence on acidosis in the adult dog, starvation acidosis is readily induced in young ones.<sup>90</sup> Glucose, injected intravenously, diminishes acetoneuria in phloridzinized dogs.<sup>91</sup> Hunger acidosis is interpreted as a carbohydrate deficiency acidosis. Adult normal dogs may show traces of acetone in hunger.<sup>92</sup>

Ehrmann<sup>93</sup> found young dogs, when undernourished, to be susceptible to his chemical, ketogenetic factors. He also observed enormous preagonal (inanition) development of ketones in diabetic dogs. Gigon<sup>94</sup> points out that allowance must be made for the fact that the carnivorous dog has accustomed itself to "metabolic tolerance" of carbohydrate withdrawal; also that, in consideration of its body weight, total acetone value of from 0.2 to 0.3 gm. per diem are very high. Von Noorden<sup>95</sup> takes the same view with reference to acquired toler-

ance toward carbohydrate withdrawal, and has *often noted the same phenomenon clinically in human beings*. He also points out that man often shows a high degree of ketonuria, even when fed such large quantities of carbohydrates (from 50 to 100 gm. per diem) as would promptly control starvation acidosis of a non-diabetic.

Again, if a dog be fed for a long period on much bread, and then be put suddenly on pure meat diet, strong acidosis develops. Heavy protein feeding has a ketogenetic influence on man also, even to the point of danger.<sup>96</sup>

We have, then, a marked parallelism between all these phenomena in man and dog, and from these researches and my own observations, I believe there is no basic difference between the acidosis of a diabetic dog and that of man.

#### B. CHOICE OF TYPE OF DIABETES

The question arises as to the *form* of diabetes most appropriate. As Macleod<sup>97</sup> points out, there is practically but one form of permanent hyperglycemia, and, of special relevance to our problem, only one form of experimental diabetes "which can be considered as analogous with the severer forms of the disease in man," namely, that following total pancreatectomy. It also seems that Leschke's<sup>98</sup> dictum, "In view of the intermittent character of the glycosurias, which arise through partial extirpation of the pancreas, no conclusions can be drawn as to the influence of any medicinal drug on glycosuria," applies equally well to an investigation of the effect of ketonuria. Certainly in view of the fluctuation known to occur in the glycosuria and ketonuria of partial pancreatectomy, the logical *first* phase of such an investigation is on the completely diabetic animal.<sup>99</sup>

#### C. TECHNIC OF PANCREATECTOMY

Twenty-three extirpations were done essentially by the method used by Minkowski and Witzel,<sup>100</sup> all the later ones by Hédon's technic<sup>101</sup> in two stages, dislocating a lobe of the processus uncinatus amounting to about one-sixth to one-tenth the total volume of the pancreas, to a subcutaneous position, with preservation of the vascular pedicle, and, later, extirpation of this. Hédon<sup>101</sup> is certainly correct in maintaining that failure to obtain the concomitant symptoms — as polyphagia, polyuria, wasting — and, he might have added, the dextrose-nitrogen ratio of 2.8 or above, is certainly due to *incomplete* extirpation. Of course, pyogenic infection will lower the dextrose-nitrogen ratio.

#### D. METHOD OF APPLICATION OF OPOTHERAPY

All *parenteral* routes have been rejected, in view of the following considerations:

1. The complications attendant on these methods — as constitutional disturbances, with chills, fever, etc. — all inevitably associated with depression of general metabolism, and hence easily giving rise to erroneous deductions and conclusions.

2. The possibility that parenteral, and especially subcutaneous, administration may reproduce, more or less accurately, the toxic syndrome of "acute pancreatic poisoning," thus complicating the interpretation by introducing factors far removed from the physiologic norm, and hence not only having no relation to true opotherapy (which must seek to approximate physiologic conditions), but even tending to obscure any such associated specific action.<sup>102</sup> Lattes<sup>103</sup> believes that activization and passage of the tryptic ferment into the blood are possibly responsible for these sudden metabolic deaths.<sup>104</sup>

3. Perfusions of isolated organs were discarded on the basis of such conclusions as that of Ringer and Fraenkel,<sup>105</sup> who deplore the artificiality of this method and its departure from physiologic conditions. Verzar and Fejer too have given expression to very cogent reasons for mistrusting this method, at least where problems of general metabolism are at stake. The organism as a whole may comport itself quite differently from the isolated organ.<sup>106</sup> Dakin and Dudley<sup>78</sup> also show that such researches as have been already conducted along this line with pancreatic extracts are of doubtful interpretation.

#### E. GENERAL EXPERIMENTAL PRECAUTIONS

1. All dogs were discarded in which any postoperative suppuration or infection persisted. Any such process may lower glycosuria, and also undoubtedly disturb other factors.<sup>107</sup>

2. The dogs used were females; not very large; especially not deep chested; not fat; weight about 6 to 8 kg.; adult, but not old; free from disease, especially mange and distemper; best of all, animals immune to distemper through previous infection. In one series of nine I used a prophylactic vaccine furnished through the kindness of Dr. James W. Jobling and Dr. Carroll Bull, prepared by isolating the *Bacillus bronchosepticus* (Ferry<sup>108</sup>) from the blood of several actively distempered dogs. Those animals which recovered from the effects of the powerful vaccine were apparently immune. All animals with gastrointestinal disorders were rejected.

3. Before the pancreatectomy the urine was examined at least two days for sugar, etc.

4. Before the total pancreatectomy (or the second stage of the Hédon) the dog was brought into approximate nitrogen equilibrium (metabolic cages).

I soon learned to avoid long preoperative confinement of animals to the cage, and, by the Hédon method, was able to feed the animals



even on the day of the second operation. Preliminary starvation (necessary for the old Witzel technic) interferes with metabolic work.

#### F. CHEMICAL AND ANALYTICAL METHODS

1. Presence and nature of reducing bodies by Haines or Fehling; polariscope; fermentation; phenylozazones. Quantitative sugar by Bang;<sup>109</sup> later by new Benedict,<sup>110</sup> often controlled by polariscope.

2. Ammonia nitrogen by Folin;<sup>111</sup> ammonia nitrogen plus amino nitrogen by Malfatti.<sup>112</sup> Total nitrogen by Kjeldahl.

3. Aceto-acetic qualitative by ferric chlorid; also Hurtley's test<sup>113</sup> and Ondrejovich.<sup>114</sup> The ferric chlorid was almost invariably negative. Acetone qualitative by Langes<sup>115</sup> di-nitroprussid.

4. Quantitative "total acetone" by the Messinger-Huppert method;<sup>116</sup> also at times checked up by Neuberg's modification of Messinger's method; but the results tallied closely. I felt justified in using the easier "total acetone," rather than the more difficult beta-oxybutyric acid determination, since Gigon<sup>117</sup> has shown the constant relationship which subsists, *in a given individual*, between excretion of acetone and of beta-oxybutyric acid. Embden and Schmitz' warning<sup>118</sup> to avoid drawing over ammonia or other bodies fixable by iodine was carefully heeded.

5. Hepatic glycogen was only twice determined, and only by the method of Pflüger.<sup>119</sup> This omission was justifiable because (a) the dextrose-nitrogen ratios indicated total diabetes; (b) after the first ten or fifteen operations the extirpations were with certainty technically *total*; (c) even on the assumption that small fragments or accessory pancreases had escaped observation in a few animals, the general tenor of the results is dependent not at all on the presence of a total diabetes. The conclusions are valid for a *severe* or *total* diabetes. Several of the later experiments, indeed, as will be seen, purposely represent incomplete extirpations, with no glycosuria on meat diet.

In the two cases in which hepatic glycogen was determined, the figures showed a practically complete absence of all glycogen. In one (Protocol 5) a 186-gm. liver contained 0.12 per cent., or 0.22 gm. glycogen. In the other (Protocol 6) a 247-gm. liver contained 0.08 per cent., or 0.197 gm. glycogen.

#### G. GLUCOSE THRESHOLD IN DOGS

The dextrose threshold of *normal* dogs is variable, but in general runs from 3 gm. per kilogram weight (Hofmeister's figures) up to from 11 to 16 gm. per kilogram weight (Pflüger's). Relation to other food taking is important, as when given alone the average tolerance is probably 4 or 5 gm.; when given with other food, 10 gm. or over.<sup>120</sup>

## IV. PROTOCOLS

*Adult* normal dogs show no ketone-excretion on pancreas feeding, or, indeed, on any dietetic regimen. This was verified on several normal controls, observed carefully for many weeks. Thus the "total acetone" was determined on Dog 7 for a period of one month. During this time there were administered two heavy feedings of pancreas, with no rise in the total acetone figure, the latter showing, throughout the month, the usual variation of normal dogs, from 0.002 to 0.01 gm. per diem for animals of 5 to 12 kg. weight. Since immature and adolescent animals were not used in these experiments, only *adult controls* were used.

With regard to the effects of *starvation*, adult dogs show no increase of "total acetone," even on prolonged starvation. Elias and Kolb<sup>92</sup> have already shown that young normal dogs respond to starvation by ketonuria.

Adult, totally diabetic dogs show no appreciable effect of starvation on acidosis, until the starvation has been prolonged to the point of inanition, which means absolute starvation for at least five or six days. This is illustrated by Protocols 1 and 2.

## PROTOCOL 1.—Dog 35.—TOTAL EXTIRPATION, JUNE 19, 1913

Date	Food	Total Acetone	Weight
June		gm.	kg.
18-19	400 gm. beef	.012	15.4
19-20	None	.0167	...
20-21	None	.0366	...
21-22	1 liter milk	.078	15.2

## PROTOCOL 2.—Dog 31.—TOTAL EXTIRPATION, MARCH 14, 1913

Unable to retain any food after pancreatectomy. Water taken in moderate amounts.

Date	Total Acetone	Weight
March	gm.	kg.
12-13	.0021	4.2
13-14	.0044	...
14-15	.0113	...
15-16	.0521	...
16-17	.0643	...
17-18	.0517	4.0
18-19	.0608	...
19-20	.0710	3.8
20	death (inanition)	

Lüthje<sup>121</sup> also incidentally shows<sup>122</sup> that there is very little starvation acidosis in adult, depancreatized dogs.

Protocols 1 and 2 serve to illustrate another general observation, namely, that after total pancreatectomy the total acetone figures *always* rise moderately, irrespective of feeding or of starvation. The figures for normal dogs vary between 0.002 and 0.01 gm. per diem for dogs of from 5 to 12 kg. weight. After total extirpation these rise to from 0.01 to 0.09 gm. for dogs of this size. The increase is rather gradual

and progressive, and will not go much above 0.09 gm. on mixed diets, or on starvation.

PROTOCOL 3.—TOTAL PANCREATECTOMY (SECOND STAGE) JULY 3, 1913, OF DOG 50, WHICH COULD RETAIN NOTHING BUT WATER UNTIL DEATH

Date	Total Acetone	Weight
July	gm.	kg.
2-3	.002	4.4
3-4	.0078	...
4-5	.009	...
5-6	.038	4.2
6-7	.0309	...
7-8	.077	...
8-9	.472	3.8
9 death		

In the case of Dog 50 (Protocol 3), as occasionally, there was an immense preagonal increase. Preagonal decrease almost to the zero mark was sometimes observed.

We cannot doubt from the observations of Elias and Kolb<sup>92</sup> on young, normal animals that if young, diabetic animals had been used, the diabetic acidosis would have increased under starvation.

Aside from such controls, the general plan of the experiment was to place animals of known weight on diets so chosen as to satisfy calorific requirements, and then to replace, for definite periods, a part or all the protein by isodynamic amounts of pancreas (or liver, etc.), noting the influence on ketone excretion. It soon became apparent that the matter of control diet (that is, the food regimen of the days on which no pancreas was given) was very important, if one were to avoid confusing results and fallacious deductions. Much time and many animals were lost in the slow working out of these considerations. The earlier experiments showed that high protein food of any sort in a diabetic animal exerts a decided ketogenetic influence. Hence the necessity arose of preceding the feeding of pancreas by a diet including some other protein isodynamically the equivalent of the pancreas to be fed. After preliminary essays of a basal mixed diet, it was soon thought best to use a straight protein diet of lean meat. This was suitable for the carnivorous dog, and, in the form of lean, hind shank of beef, possessed the additional advantage of permitting protein and nitrogen content to be easily controlled. Later, dextrose and fat were added to the basal diet in some of the experiments. In general, a moderate excess of protein food constituted the fundamental diet.<sup>123</sup>

It became evident from the earlier experiments in which no quantitative determinations of ketones were made, the intensity of color reactions being relied on, that on a moderately high protein diet of lean beef after total pancreatectomy, ketonuria sometimes developed, but with moderate intensity and rapidity, while the reaction to pancreas feeding was prompt, and marked by extreme development of aceto-

nuria. In Protocol 4, only the qualitative tests were invoked, but these were carefully done, and included, each day, the various modifications of the di-nitro-prussid-alkali test for acetone; and the Gerhardt (ferric chlorid), Hurltley<sup>113</sup> and Ondrejovich<sup>114</sup> (iodin) methods for aceto-acetic acid. On the twelve control days preceding the extirpation there was never a trace of acetone or aceto-acetic acid demonstrable. After the pancreatotomy, on diets varying between beef or dextrose, or beef and dextrose, there were no demonstrable ketones, but on the third and fourth twenty-four-hour periods (postoperative) there developed, following the administration of raw beef pancreas in doses of 30 gm., a positive acetone test, and on the tenth period, following a dose of 125 gm., positive acetone and diacetic reactions. At these two periods the ammonia-amino (Malfatti) jumped up also, as usual in ketonuria, from 0.183 and 0.177 gm. to 0.42 gm. and to 0.438 gm.

Protocol 4 illustrates the same result.

PROTOCOL 4.—DOG 6.—TOTAL EXTIRPATION, NOV. 22, 1912

Date	Food	Acetone	Diacetic	Weight kg.
Nov. 20-21	400 gm. lean beef	0	0	13.3
21-22	{ 400 gm. beef	0	0	....
	{ 10 gm. dextrose			
22-23	No food	0	0	....
23-24	80 gm. beef	0	0	....
24-25	120 gm. beef	0	0	13.2
25-26	200 gm. beef	0	0	....
26-27	200 gm. raw beef	++	+	....
	<i>pancreas</i>			
27-28	200 gm. beef	0	0	13.2

Such results, diametrically the opposite of what I had anticipated, since I was not familiar with the literature of pancreatic opotherapy, were so striking that it was decided to investigate the matter by quantitative methods. Protocol 5 is a specimen.<sup>124</sup>

PROTOCOL 5.—DOG 27, TOTAL EXTIRPATION, MARCH 5, 1913

Date	Food	Total N Intake gm.	Qual. Acetone	Total Acetone gm.	Weight kg.
March 2-3	400 gm. beef	13.0	0	.0082	7.5
3-4	400 gm. beef	13.0	0	.0098	...
4-5	Starved	0.0	0	.0034	...
5-6	50 gm. beef	1.62	++	.1191	...
6-7	{ 150 gm. beef	4.87	++	.1556	7.4
	{ 20 gm. potato				
7-8	{ 400 gm. beef	13.0	++	.1406	...
	{ 25 gm. dextrose				
8-9	{ 140 gm. meat	4.80	++	.187	...
	{ 50 gm. bread				
9-10	200 gm. beef	6.5	Trace	.097	...
10-11	200 gm. beef	6.5	0	.044	...
11-12	200 gm. fresh pancreas	5.38	+++	1.137	...
12-13	None	0.0	+++	0.495	7.1
13-14	None	0.0	+++	0.297	...
14-15	150 gm. beef	4.87	+	0.1068	7.1

The dextrose-nitrogen ratio confirmed my operative assumption that the pancreatectomy was total.

This table, as many others, illustrates the fact that in total diabetes, ketonuria develops on feeding of high protein in *any* form of meat, but to a much greater extent on raw pancreas. Thus we find total acetones of from 0.1 to 0.4 gm. per diem (for dogs of from 6 to 12 kg.) developing on beef diet, but of 0.3 to 0.6 to 1.0 on dynamogenetically equivalent amounts of raw pancreas. There is considerable individual variation in ketogenetic response; thus one animal may show as great a quantity of total acetone on beef feeding as another does on pancreas; hence it would be misleading to compare the quantitative results (or color reaction) of one dog on pancreas feeding with those of another on muscle feeding. In general, severely or totally diabetic dogs will not develop a *qualitative* acetone (color) reaction after several days' starvation or low diet or on a mixed diet not much above calorific requirements, but will rapidly develop it on high protein, and much more rapidly and intensely on protein-equivalent quantities of raw pancreas.

In some dogs, on moderate or high beef-muscle diet, the qualitative reaction is so marked that the change to pancreas does not render it more intense, inasmuch as it has already a maximum intensity for a color reaction. In such cases, however, the quantitative determinations always show the difference plainly (Protocol 6).

PROTOCOL 6.—DOG 54, SEPT. 11, 1913, SECOND STAGE OF HÉDON TOTAL PANCREATECTOMY

Date	Food	Protein N Intake gm.	Qual. Acetone	Total Acetone gm.	Weight kg.
Sept. 10-11	450 gm. beef	14.61	0	0.01183	4.6
11-12	Starved	0.0	0	0.0230	
12-13	400 gm. beef	13.0	0	0.0640	4.7
13-14	350 gm. beef	11.36	0	0.0721	
14-15	{ 400 gm. raw pancreas	10.76	+++	0.385	
15-16	{ 350 gm. beef 400 gm. raw pancreas	11.36	+++	0.124	
16-17	{ 100 gm. beef tallow	13.00	+++	0.623	4.5
17-18	350 gm. beef	11.36	+++	0.2375	
18-19	350 gm. beef	11.36	+++	0.1942	
19-20	400 gm. pancreas	13.00	+++	0.487	
20-21	350 gm. beef	11.36	+++	0.3722	
21-22	Refused food	0.0	+++	0.340	

Here, after the maximum *qualitative* reaction had appeared after pancreas feeding, it remained essentially unchanged to the end. In general, the aceto-acetic reaction develops only if the acetonuria is intense; this applies especially to the ferric chlorid test, the more deli-

cate Hurltley and Ondrejovich tests being positive with lesser degrees of acetonuria.<sup>125</sup> The development of the aceto-acetic reaction as well as other points is illustrated in Protocol 7.

PROTOCOL 7.—Dog 67, Nov. 28, 1913, SECOND STAGE OF HÉDON  
PANCREATECTOMY

Date		Protein N Intake	Qual. Acetone	Ferric Chlorid Reaction	Weight kg.
Nov.	Food	gm.			
27-28	350 gm. beef	9.74	0.0026	0	9.2
28-29	None	0.0	0.0029	0	...
29-30	350 gm. beef	11.36	0.079	0	...
30-1	350 gm. beef	11.36	0.104	0	...
1-2	350 gm. beef	11.36	0.0386	0	...
	{ 20 gm. dextrose				
	{ 40 gm. fresh				
	{ dog				
2-3	{ pancreas	7.59	0.638	+	9.3
	{ 200 beef				
	{ 20 dextrose				
3-4	{ 350 beef	11.36	0.0603	0	...
	{ 20 dextrose				
4-5	{ 350 beef	11.36	0.0504	0	...
	{ 20 dextrose				
	{ 80 gm. fresh				
	{ dog				
5-6	{ pancreas	11.94	0.542	+	9.0
	{ 300 gm. beef				
	{ 20 gm. dextrose				
6-7	Vomited all food	0.0	0.420	+	8.7
7-8	Vomited all food	0.0	0.438	+	...
8-9	Vomited all food	0.0	0.0752	0	8.4
9	Death with edema and coma				

Dog 67 was totally diabetic, its dextrose-nitrogen on the 30th being 3.05. It was on a high protein diet, its weight having been about 9 kg. and its daily lean meat ration from 200 to 350 gm. It illustrates well the action of raw pancreas, and shows that the latter is not cloaked or inhibited by concomitant feeding of dextrose. This and other protocols do, however, seem to indicate that heavy doses of pure dextrose tend to *lessen* acidosis even in dogs. Thus note that on the 30th and 1st the total acetone is 0.104 gm. on beef alone; on the next day it is 0.0386 on the same amount of beef plus 20 gm. sugar. Days 3-4 and 4-5 show the same influence, and I have several times noted this same effect. Compare Protocol 5 above, on days 6 to 9.

Inasmuch as theoretical considerations would lead us to expect more from a hepatic than from a pancreatic organotherapy in diabetes, experiments were also conducted along this line, starting with the expectation that a lowering of dextrose-nitrogen ratio and of ketonuria would result. It was soon found, on the contrary, that glycosuria is not appreciably influenced (except incidentally by the concomitant variations in carbohydrate intake), and that raw liver is, as pancreas, ketogenetic, although not to so high a degree (Protocol 8).



PROTOCOL 8.—DOG 17, SECOND STAGE OF HÉDON PANCREATECTOMY, DONE  
 JAN. 6, 1913

Date	Food	Food N. gm.	Total Acetone gm.	Weight kg.
Jan.				
5-6	400 gm. beef	13.0	.0174	8.2
6-7	100 gm. beef	3.25	.058	...
7-8	400 gm. beef	0.13	.092	...
8-9	400 gm. beef <i>liver</i>	13.05	.364	...
9-10	400 gm. liver	13.05	.467	8.1
10-11	400 gm. beef	13.0	.302	...
11-12	400 gm. beef	13.0	.1618	...
12-13	400 gm. beef	13.0	.283	...
13-14	300 gm. beef and dextrose 20 gm.	9.74	.124	8.1
14-15	{ Beef <i>pancreas</i> 350 gm., dextrose 20 gm.	9.45	.6023	8.0
15-16	Rejected all food	0.0	.1426	...
16-17	Rejected all food	0.0	.122	7.9
17	Death			

It had seemed possible that beef muscle was less ketogenetic than beef pancreas on account of a possible inhibiting influence of the higher glycogen content of the former, but this explanation was rendered invalid by the results of liver-feeding, for liver possesses a much higher glycogen content than does muscle, yet it has decidedly greater ketogenetic properties. I also ascertained by direct experiment (Dog 53) that the feeding of 1 gm. of pure glycogen concomitantly with the pancreas did not inhibit in the least the ketogenetic action. This was, indeed, to be expected, inasmuch as the only way glycogen could exert such an effect would be by primary splitting to dextrose with absorption, and the protocols amply prove that even large amounts of dextrose (20 gm.) given simultaneously with the pancreas do not exert a marked inhibitory influence on ketone formation. (See excerpt of Protocol 7, above, especially on dates 1 to 6.)

The feeding of fats simultaneously with pancreas gives rise to more marked increase in ketogenesis than that resulting from pancreas alone.

## PROTOCOL 9.—DOG 54, TOTAL PANCREATECTOMY

Date	Food	Total Acetone gm.	Weight kg.
Sept.			
13-14	400 gm. beef	.064	
14-15	400 gm. pancreas	.385	4.7
16-17	400 gm. pancreas	.623	
	100 gm. tallow (beef)		
19-20	400 gm. pancreas	.487	

Mosenthal<sup>16</sup> explained the increased ketogenesis, which he observed in his case of severe diabetes on pancreatic opotherapy, as due to increased fat absorption. As proof he cites the fact that a phloridzinized dog (hence with normal absorption) develops ketonuria, while a totally diabetic dog (hence with fat absorption practically nil) shows none. This deduction is fallacious from two points of view: (a) In phloridzinized dogs ketonuria occurs, but only after the reserve gly-

cogen depots have been exhausted (Marum<sup>89</sup>). This shows a close relationship between ketogenesis and carbohydrate utilization, but no especial relation between ketogenesis and fat absorption. (b) Pancreatic diabetic dogs *do* develop ketosis. In the great majority of these experiments I have avoided fat food, as a complicating factor, and hence I can be positive that increased intestinal absorption of fat is not the only or the main factor in heightened ketonuria after pancreas feeding.

After ketonuria has been once precipitated, especially in a severe form, as by repeated feedings of pancreas, there persists an increased sensitiveness to ketogenetic factors, so that the ketonuria tends to persist, though in lessened intensity, even under a diet non-ketogenetic. This may be due to a permanent, toxic damage (as of the liver) brought about by the first exhibition of pancreas.

Also in several experiments, after a heavy ketonuria had been developed by pancreas feeding, it increased rapidly, the animal was very sick, vomited or refused all food, became comatose, sometimes developed edema, and died three or four days after the development of the intense ketonuria. In such cases the only positive necropsy findings were usually an enlarged liver, bright yellow in color and friable. Microscopically, such livers showed a high degree of fatty degeneration, almost to the point of complete replacement of the liver parenchyma by fat globules. None of the gastric ulcers or duodenal kinks described by Minkowski<sup>126</sup> could be found in these cases of emesis and this is probably a toxic emesis.

#### COMA DIABETICUM IN DOGS

There is considerable dispute as to the occurrence in dogs and other animals of a true coma diabeticum.<sup>127</sup> Ehrmann<sup>128</sup> discusses the differentiation between true coma and the allied states, and maintains that he obtains true coma in rabbits, by his sodium butyrates. In animals the signs and symptoms are naturally uncertain and difficult of interpretation, but if his objective criteria are valid, I certainly obtained coma in several dogs, and only in ones which had received pancreatic feeding. In those on ordinary carnivorous or mixed diet, death in inanition occurred the second or third week, but no definite coma. In a few there developed, after two or three administrations of pancreas, a narcosis-like sleep, with deep and slow inspirations and short forcible expirations. This came on early (even two or three days after the pancreatectomies) on heavy pancreas feeding, never except on pancreatic feeding, and was accompanied by great ketonuria, but usually (as in most other cases) by preagonal decrease of ketonuria to almost the zero mark. I have already referred to another type of death—the “acute pancreas death.”

One must differentiate this terminal syndrome of fatty toxic liver, ketonuria and coma from that of anesthesia liver degeneration. With the exception of the work done in the two months, December, 1912, and January, 1913, a fresh can of highest (anesthetic) purity ether has been opened for each pancreatectomy. But during that period, without the knowledge and contrary to the explicit order of the experimenter, left-over ether, kept in an ordinary bottle and exposed to sunlight, was used. The result was that practically every animal, fourteen in all, died on the fourth or fifth, or sometimes even the second or third days postoperative, displaying malaise, pernicious vomiting, and a comatose condition. The liver was always large and bright yellow. While ignorant of any toxic substances that might develop in ether under these circumstances, I feel assured that the extra burden put on the liver by pancreatectomy must in these cases have proved, in conjunction with some chemical toxins, too much for that organ. Many protocols and experiments demonstrates the slightness of the effect of an anesthesia of *pure* ether on ketogenesis. See, for example, the excerpt from Protocol 2. There is practically no postanesthetic rise in ketonuria in any case.

#### EFFECT ON GLYCOSURIA

In the earlier experiments it was thought that a reduction of glycosuria and a lowering of the dextrose-nitrogen ratio was observed on pancreatic feeding. But after a few experiments the fallacy became apparent. The food had been suddenly changed from a mixed diet containing considerable carbohydrate to one of pancreas—almost pure protein. Or where this was not the case, the attention had been focused on small chance variations in dextrosuria, incidental to all such experiments. It is certain that no lowering of glycosuria or of the dextrose-nitrogen ratio results from pancreatic feeding in totally, severely or mildly diabetic animals. I do not wish to be understood as questioning the results of Pratt, Spooner and others, with *prolonged feeding* of pancreas in milder types of diabetes.

#### MILD DIABETES

In several dogs, the size of the transplanted lobe was so regulated that a diabetes accompanied by a slight glycosuria or by a lowered threshold resulted. Thus Dog 74 (Protocol 10) displayed no glycosuria on a diet of meat, or of meat and starchy foods, or on 20 gm. dextrose with meals, but promptly developed glycosuria on 30 gm. dextrose, given with meals.

On pancreas feeding it showed slight increase of acetone, this rising from about 0.002 to 0.008 up to 0.009, 0.01 or even to 0.0974. There was an increase of ammonia-amino during the twelve to twenty-four hours immediately following such feeding, as from 0.67 gm. up to 2. 3.

or even 4.79 gm. The last figure was on feeding of 400 gm. pancreas. The preceding day, on a practically equivalent meal of 400 gm. raw beef, the Malfatti showed 0.863 gm. There was also the usual polyuria observed on pancreas feeding.

PROTOCOL 10.—EXCERPT OF PROTOCOL OF DOG 74, OPERATED ON JUNE 19. (DISPLAYED NO GLYCOSURIA ON MEAT DIET JUNE 20-JUNE 24.)

Date	Diet	Dextrose	Total Acetone gm.	Weight kg.
June				
25	Potato + bread ad lib.	Trace	.0027	8.75
26	400 gm. beef.....	0	.003	
27	Beef 400 gm.; potato ad lib.....	0	.0024	8.75
28	300 gm. beef.....	0	.0021	
29	300 gm. beef.....	0	.0080	
30	{ 67 gm. raw dog pancreas.....	Trace	.012	8.8
	{ 233 gm. beef.....			
July				
1	300 gm. beef.....	0	.0077	
2	250 gm. pancreas (beef)	+ (0.7 per cent. = 2.59 gm.)	.0092	
3	300 gm. beef.....	0	.0028	
4	300 gm. beef.....	0	.0026	
5	300 gm. + 5 gm. dextrose (simultaneously)	0	.0014	8.75
6	300 gm. beef.....	0	.0034	
7	300 gm. beef + 15 gm. dextrose.....	0	.0030	
8	300 gm. beef.....	0	.0041	
9	300 gm. beef + 30 gm. dextrose.....	++ (1.3 per cent. = 4.87 gm.)	.0026	
10	300 gm. beef + 20 gm. dextrose.....	0	.0046	
11	300 gm. beef.....	0	.0031	8.7
12	300 gm. beef.....	0	.0049	
13	300 gm. raw (beef) pancreas.....	++ (1.26 per cent. = 8.06 gm.)	.072	
14	300 gm. beef.....	Trace	.0161	
15	300 gm. beef.....	0	.0072	
16	300 gm. raw beef pancreas.....	++ (1.12 per cent. = 5.096 gm.)	.0974	8.8
17-26	300 to 400 gm. beef per diem.....	None	*	
27	400 gm. beef + 30 gm. dextrose.....	++ (3.12 per cent. = 4.99 gm.)	.0044	8.6
28	400 gm. beef.....	0	.0037	
29	400 gm. raw pancreas..	++ (1.11 per cent. = 4.5 gm.)	.0154	
30	400 gm. beef.....	++ (2.48 per cent. = 6.2 gm.)	.033	
31	400 gm. beef.....	++ (1.84 per cent.)	.050	
Aug. 1-5	400 gm. beef per diem..	Always ++	*	

\* Not estimated.

Most interesting of all, there developed a *sharp and marked glycosuria*, during the twenty-four hours following each pancreas feeding. This was present at no other time, except when over 25 gm. dextrose was given. We have invariably found, in dogs with greatly lowered tolerance but no actual glycosuria on meat diet, that the pancreas opotherapy precipitates glycosuria.

The positive dextrose findings were frequently checked up by polariscope and phenylhydrazin tests.

Similar findings as to the dextrose mobilizing power of pancreas by mouth were obtained on all animals which were mildly diabetic.

It will be noted in Protocol 10 that after the final pancreas feeding there was a persistent glycosuria. This has been observed twice. It seems probable that it falls in the same category as that increased sensitiveness of the diabetic organism to *ketogenetic* factors after repeated pancreatic opotherapy, referred to above. In all likelihood both represent a permanent toxic damage of liver or pancreas.

I am now engaged in determining whether or not the increased glycosurias of pancreatic opotherapy are accompanied by a hyperglycemia.

These influences of pancreas-feeding on ketonuria and glycosuria apply to *fresh, raw* pancreas, and to raw pancreas kept on ice for several (at least four) days, but not to *cooked* pancreas.

Several subsidiary effects of pancreatic opotherapy were noted, but are already generally familiar. Thus the ammonia was increased concomitantly with the ketonuria. Amino-acid excretion was high in severe diabetes. My earlier determinations were unreliable, for I estimated the combined ammonia and amino nitrogen by the Malfatti method, and the ammonia by the Folin method, obtaining the amino nitrogen by subtraction. I was sometimes surprised to find the ammonia figure to be greater than the figure for ammonia plus amino. It was only late in this work that attention was called to the fallacy of using alizarin as an indicator.<sup>129</sup> After this I verified the high amino nitrogen of the totally diabetic animal.<sup>130</sup>

#### V. INTERPRETATION OF RESULTS

Pancreatic feeding thus gives rise to increased ketonuria. Does that mean to increased ketogenesis? This is a pertinent question, because there is absolute clinical evidence that ketone excretion does not always run parallel to ketone formation.<sup>131</sup> Those who champion the causal relation between ketones and coma diabeticum lay special emphasis on the toxicity of the non-eliminated fractions accumulating in the blood and tissues, this being true whether their toxicity is due

simply to their acidity (Naunyn) or to a specific quality. Again, exhibition of alkalis certainly increases excretion of the bodies.<sup>132</sup>

But there is nothing in the behavior of our animals which would lead us to suspect that ketones are being generated and accumulated before the administration of pancreas, the latter simply increasing their excretion. In such case we should certainly have found at least some moderate increase in ketonuria prior to the opotherapy. In most of the experiments, the pancreas was given at an earlier period after pancreatectomy than one ever sees ketonuria developing on ordinary mixed or even raw beef diet. Moreover, there was no evidence that these dogs were suffering from ketone poisoning (if such an entity exists) prior to opotherapy. Also the toxic symptoms exhibited by the dogs appeared with, and increased in proportion to, the development of ketonuria. And in several of them there was what I interpreted as a real coma, with tremendous amounts of ketone bodies. This parallel development of ketonuria and toxic symptoms puts the burden of proof on those who would contend that the ketones were formed in the tissues early and excreted only under the influence of the pancreatic opotherapy. If one accepts the hypothesis of Embden and Michaud,<sup>133</sup> according to which diacetic and beta-oxybutyric acids are *physiologic*, intermediary products or by-products of the formation of carbohydrates from fat, normally oxidizing to end-products before elimination, but appearing as such in the urine when, on carbohydrate deficiency, fat catabolism oversteps the bounds, then what I have just contended holds true, *mutatis mutandis*, so that even on this doctrine, there is no reason to believe that before opotherapy there were stored up in the tissues such unoxidized ketone bodies.

By what mechanism does pancreas feeding increase ketogenesis? Any attempt to answer this must take into account the factors which influence the production of acetone bodies ordinarily, that is, in the absence of pancreatic opotherapy.

With regard to their ultimate chemical source there is overwhelming accord that they largely arise in the course of intermediary metabolism, from the vitiated splitting of fats.<sup>134</sup> However, one must concede the possible derivation of a portion of the ketones from protein.<sup>135</sup>

This being their ultimate source, what are the contributory or predisposing factors in ketogenesis?

First, and very obviously, *diabetes*. But the limitation of our knowledge in the field of pathophysiology is so great that the word "diabetes" can at present connote but little definite in this sense.

Second, and more concretely, *increased utilization of fats*.<sup>136</sup> Fats are, for the diabetic organism, ketogenetic.

Third, *deficient utilization of carbohydrates*.<sup>137</sup> Of course, the diabetic organism furnishes the most conspicuous example of func-



tional incapacity for handling carbohydrates. According to the interpretation now most current, there follows on this reduced consumption of sugars a compensatory increase of catabolism of body-fat and protein by way of response to calorific demand, such hypermetabolism then resulting in a false degradation of body fats, and possibly to a lesser extent of proteins (Landergren), ending in ketone formation.<sup>138</sup>

Other minor contributory factors must be mentioned. Thus *young* dogs (and human beings) are more susceptible to the action of any of the influences mentioned, especially carbohydrate deprivation.<sup>92</sup> Also a lessened store of hepatic glycogen predisposes to ketogenesis. This is probably a specific phase under the general factor of lowered carbohydrate utilization; indeed, it *may* be the fundamental mechanism of the latter.<sup>89</sup> The degree of acidosis bears no fixed relation to the degree of glycosuria.<sup>79</sup> In phloridzinized dogs a preservation of the nitrogen equilibrium ensures freedom from acidosis; starvation precipitates it; ingestion of sugar prevents it.<sup>139</sup> What light does this consideration of factors influencing ketogenesis throw on the mechanism by which pancreatic opotherapy increases it?

1. It is probable that feeding of pancreas may augment ketogenesis by determining *increased absorption of fat*. The latter has been proved to be usually greatly impaired when the pancreas is badly diseased or partially extirpated, experimentally or for disease.<sup>140</sup> The evidence, while not unanimous, points strongly to the conclusion that absorption and nutrition are considerably improved by raw pancreas feeding, and this seems to hold for the insufficiency arising from (a) incomplete or complete extirpation,<sup>141</sup> (b) supposedly complete exclusion of external pancreatic secretion from the intestine,<sup>142</sup> and (c) organic pancreatic disease.<sup>143</sup>

The question as to the precise nature of the mechanism through which the pancreas exerts this undeniable influence on fat-absorption is too complex to be analyzed here except cursorily. That influence seems not to be attributable to any known direct effect or character of the external secretion, such as emulsifying power, alkaline content, lipolytic-enzyme content, or to any indirect effect exerted on associated digestive processes, as by controlling the secretion or activity of bile, or the intestinal motility.<sup>144</sup> Lessened digestion of fats is not the solution, since it is certain that the splitting of food fats is but little or not at all impaired in pancreatic insufficiency.<sup>145</sup> Yet there is considerable evidence that pancreatic juice is in some way necessary for absolutely normal fat resorption.<sup>146</sup> As concerns the possible action of *internal* secretion, it is also doubtful whether the pancreas influences fat absorption through its effect on carbohydrate metabolism. Certainly any relation between hyperglycemia and vitiated absorption may be ruled

out.<sup>147</sup> Another allied concept, but of rather vague significance, is that lowered fat absorption is simply a part of the general depressed metabolism of severe diabetes (Allen). Finally, Lombroso has ably championed the view that a special pancreatic hormone exerts a control over the absorption of fat, and possibly its intermediary metabolism.<sup>148</sup> In increase of fat absorption we have a partial explanation of the augmented ketogenesis on pancreas feeding. In those of our experiments in which fats were given concomitantly with pancreas, there was such an increased ketone excretion as to justify the deduction that this may be one etiologic factor, more especially in the mixed diet of the usual diabetic regimen. However, the results cannot be interpreted altogether along this line, because I have, in many experiments, avoided any possible absorption food fats.

2. The degree of *protein absorption* is a possible factor. This is certainly decreased in pancreatic insufficiency and improved on pancreatic feeding.<sup>149</sup> In the removed pancreas (used for opotherapy) trypsinogen is speedily converted into trypsin. Thus, fed pancreas not only has a high protein content per se, but also may help in digestion and absorption of any other food protein. It is certain from the results of the present work that several of the raw protein foods (beef, pancreas, liver) are ketogenetic to the diabetic organism. But whether or not this is a property of the protein, as such, depends on the extent to which proteins are an ultimate chemical source of ketones. There is reason to believe that the rôle is inconsiderable (see above).

3. Almost certainly the ketogenetic properties under discussion are *toxic*, probably owing to autolytic substances which are normally destroyed by the pancreas (detoxicating theory of pancreatic function). This is along the line of Reach's<sup>150</sup> interpretation of the increased glycosuria and hyperglycemia after feeding of raw meats. Such glycogenetic and ketogenetic toxins are probably non-specific for pancreatic tissue, but present in greater quantity in pancreas, or else in a more potent form than in liver or in muscle tissue. They may be conceived of as exerting their ketogenetic influence in many different ways, but most plausibly by deranging the hepatic function.<sup>151</sup>

4. Could the increased ketogenesis be secondary to decreased utilization of carbohydrates? Probably not. For the overwhelming evidence is that opotherapy does not decrease the burning of sugar (see above). Moreover, most of my animals were *totally* diabetic, and hence already oxidizing a minimum of carbohydrates.<sup>152</sup> Of course, those authors certainly go too far who deny any controlling influence of carbohydrate metabolism on ketone-formation in carnivora. Marum's<sup>89</sup> important observation that in phloridzinized dogs acidosis occurs only after the reserve glycogen has been consumed proves this. But it is

undoubtedly true that the correlation between acidosis and carbohydrate non-utilization is not nearly so close in the dog as in man. The adult dog is "accustomed" (von Noorden) to bear carbohydrate deprivation without reacting by acidosis. Allard<sup>81</sup> has specifically shown that the dog does not readily respond to low carbohydrate by acidosis. My experiments repeatedly show that feeding of dextrose in heavy doses does not lessen the acidosis appreciably, once it is developed. Apropos of this possible relation of acidosis to depressed sugar metabolism, it occurred to me near the close of these experiments that the glycogen present in the skeletal muscle might be responsible for the lesser ketogenetic activity of fed muscle, as compared with that of pancreas. But the two experiments on liver-feeding showed that this may be ruled out as a factor, for the liver of a normal dog has a high glycogen content, and yet the ketogenetic response was almost as marked as in the case of pancreas. Pancreas contains only a trace of glycogen. Feeding of glycogen alone gave rise to no increase or decrease of acetone excretion, as was indeed to be anticipated, inasmuch as glycogen, like starch, must be split to disaccharids and monosaccharids before absorption; and we know the latter are not as markedly antiketogenetic in carnivora as in man.

5. Finally, it seems conceivable, although not probable, that, in pancreatic opotherapy, *enzymes* are introduced which stimulate the tendency to ketone formation already present; or expressed more precisely, catalytics, which accelerate the mass-action tendency already inherent in a diabetic organism to vitiated catabolism of fats (perhaps also of proteins), with consequent ketogenesis. I here refer to ferment action on *intermediary* metabolism, for Reach<sup>160</sup> has already excluded the local action of external secretion ferments in increasing fat absorption. There is also the possibility that this opotherapy acts by mobilizing tissue fats, giving rise to increased intermediate metabolism of endogenous fat; the vicious splitting of such fats in the totally diabetic organism would then give rise with certainty to ketones.

## VI. SUMMARY

In the severe or total pancreatic diabetes of dogs, ketonuria of sufficient intensity to be demonstrable by the qualitative tests always develops provided the animal survives several days, and is on a diet covering its calorific requirements.

The "total acetone" figures for adult normal dogs of from 5 to 12 kg. weight run about 0.005 to 0.01 gm. per diem.

After total or near total pancreatectomy and on complete starvation (except for water), there is a slight gradual increase to about 0.01 gm. up to 0.09 gm. per diem.

By judicious administration of a low calorie mixed diet after pancreatectomy the total acetone figures may be kept down to about the latter limits.

Heavy protein diets of any sort exert a ketogenic influence on the diabetic organism. Thus the feeding of an exclusive protein diet of lean beef for several days invariably precipitates a ketonuria appreciable by ordinary qualitative tests, the total acetone going up to 0.1 to even 0.4 gm.

On dynamogenetically equivalent amounts of raw pancreas the total acetone always increases greatly to 0.5 to 0.7 or even over 0.1 gm. per diem, which represents tremendous amounts for dogs; the color reactions have a maximum intensity. Such increases occur on a single feeding of pancreas. The feeding of raw liver is responded to by a greater ketonuria (0.3 to 0.4 gm.) than that following muscle feeding, but not nearly so marked as the reaction after pancreas. These differences were proved to be *not* due to variations in protein content or in glycogen content.

I doubt whether this ketogenic influence of pancreatic opotherapy is altogether specific. Yet, in view of the consideration that it is so much greater for pancreas than for other representative protein foods we cannot deny the possibility of its being specific.

As to the mechanism of its action, I have shown that it is not referable to increased absorption of protein or of fats, although both these are factors in additional increase of ketogenesis. It may be associated with increased intermediate metabolism of body-fat; I have not attempted to prove this. It is probably a *toxic* action, comparable to the increased glycosuria demonstrated by Reach<sup>150</sup> on pancreas feeding. Doubtless such toxic influences are largely directed toward the hepatic functions.

If views as to the nature of diabetic acidosis be classified into two groups (Allen<sup>155</sup>), namely (*a*) those maintaining that this is a condition *sui generis* (von Noorden and others) and (*b*) those holding it to be due solely to carbohydrate deficiency (Landergren, Forssner, Gigon), then I believe the present experiments tend strongly to show that "acidosis" in dogs may vary independently of the status of carbohydrate ingestion and metabolism.

#### VII. CONCLUSION

With reference to the practical aspect of pancreatic organotherapy, Allen<sup>153</sup> remarks, "All authorities are agreed upon the failure of pan-

creatic opotherapy in diabetes. The attempts are continued because of the strong theoretical inducements."

On the contrary, after ruling out all doubtful cases and false interpretations, there seem to be a few exceptions to this dictum, namely, cases of diabetes associated with deranged absorption of fats and proteins; and it is only the administration of *unheated* pancreatic emulsion or extracts, including pankreon, by *feeding* which seems to be of avail here. Moreover, both glycosuria and acidosis are increased, and yet, under careful control, this therapy seems to have been, in selected cases, of some benefit.<sup>154</sup>

With reference to their theoretical bearing, these negative results of organotherapy have been repeatedly invoked by the opponents of the doctrine of pancreatic internal secretion (Pflüger, Leschke and others) as effectually negating that hypothesis. But it is metaphysically speaking, one thing not to have proved a doctrine, quite a different thing to have disproved it. We may possibly agree with Hédon's<sup>27</sup> aphorism that the existence of a pancreatic internal secretion will only then have been *demonstrated* when it shall have been possible to check diabetes of a depancreatized dog by some form of pancreatic opotherapy. But we can never consider it *disproved* until the cause of the negative results has been fathomed; as Pflüger remarks, "Negative proofs in themselves have no final force unless the proof shows why they are negative."<sup>155</sup>

Moreover, aside from the philosophical aspect, it is possible to assign several specific reasons for anticipating such negative results. Thus, as Verzar and Fejer<sup>156</sup> aptly remark, "A negative result can be occasioned by various other causes. Thus to mention only one possibility, the amount supplied in this manner to a body from which the pancreas hormone has entirely vanished may be too small to reach a concentration sufficient for the oxidation of sugar."

We have always the undisputed fact staring us in the face that when the pancreas is extirpated a total diabetes is precipitated; and that when a small part of that organ is left in the blood circuit, but otherwise separated as to all organic continuity (even nervous) from the rest of the animal, the latter is yet preserved from diabetes (Lombroso). Biedl<sup>157</sup> is justified in contending that "the entire data on pancreas diabetes . . . testifies decidedly that here an internal secretion of the pancreas is lacking which normally plays a decisive rôle in carbohydrate metabolism."

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121. Luthje: Deutsch. Arch. f. klin. Med., 1904, lxxix, 498.
122. For instance, Table 1, p. 501.
123. It is notoriously difficult to obtain nitrogen equilibrium in carnivores unless enormous amounts of protein food are given, since the protein tolerance increases, advancing to higher and higher levels (Lusk, Graham: The Science of Nutrition, Philadelphia, Saunders, 1909, pp. 110, 111).

124. In interpreting the tables given below, it must be remembered that there is no discrepancy between a "total acetone" figure of, say 0.0082 gm., and a *negative* qualitative acetone or diacetic test. For even the very sensitive Reynolds' test reacts only with 0.01 mg. in 1 c.c. water—which is about the equivalent (taking 400 c.c. as an average twenty-four-hour urine for a diabetic dog) to 0.004 gm. for twenty-four hours. All these qualitative tests are less sensitive when applied to *urine*, especially dogs' urine and particularly diabetic dogs' urine, than when applied to an aqueous solution of ketones, because of the high pigmentation of the former. The test used here (Legal-LeNobel-Lange) is not quite so sensitive as Reynolds' (Abderhalden: *Handbuch der biochemischen Arbeitsmethoden*, 1910, iii, Part 2, pp. 900-913). In general, varying of course with the concentration of the urine, a "total acetone" of below 0.09 gm. per diem will not give a qualitative color reaction to acetone. A diacetic (ferric chlorid) test will usually not be obtained with a "total acetone" much below 0.1 gm. per diem. These figures are for totally diabetic dogs, which usually run from 300 to 700 c.c. urine per diem. They correspond to about a 0.0225 per cent. (or 1:4,500) acetone solution, and to about a 0.025 per cent. (or 1:4,000) aceto-acetic solution. However, my use of the quantitative measurements does away with the necessity of emphasizing qualitative results.

125. Labbé (Rev. de méd., 1912, pp. 257, 374), as also Azémar, cited by him, usually found acetone, but no diacetic acid in diabetic dogs.

126. Minkowski: Arch. f. exper. Path. u. Pharmakol., 1893, xxxi, 182.

127. For literature see Gigon (Footnote 94).

128. Ehrmann: Berl. klin. Wchschr., 1913, I, 12.

129. Macadam: Jour. Path. and Bacteriol., 1913, xviii, 284.

130. Galambos and Tausz: Ztschr. f. klin. Med., 1913, lxxvii, 14. Loeffler: Ztschr. f. klin. Med., 1913, lxxviii, 483.

131. Magnus-Levy: Arch. f. exper. Path. u. Pharmakol., 1899, xlii; Ergebn. d. inn. Med. u. Kinderh., 1908, i, 352.

132. Ehrmann: Berl. klin. Wchschr., 1913, I, pp. 11, 65.

133. Embden and Michaud: Biochem. Ztschr., 1908, xii, 262.

134. Magnus-Levy: Ergebn. d. inn. Med. u. Kinderh., 1908, i, 352. Gigon: Ergebn. d. inn. Med. u. Kinderh., 1912, ix, pp. 285-295. Von Noorden: (Footnote 95).

135. Landergrén: Nord. med. Ark., 1910, Part 2, No. 10, cited by Gigon: Ergebn. d. inn. Med. u. Kinderh., 1912, ix, 206. Embden and Engel: Beitr. z. chem. Phys. u. Path., 1907-8, xi, 323.

136. For literature see Hammarsten (Footnote 88). Magnus-Levy: Ergebn. d. inn. Med. u. Kinderh., 1908, i, 352. Gigon: Ergebn. d. inn. Med. u. Kinderh., 1912, ix, 206. Forssner: Skandin. Arch. f. Physiol., 1910, xxiii, 305. Landergrén: Nord. med. Ark., 1910, Part 2, No. 10, cited by Gigon: Ergebn. d. inn. Med. u. Kinderh., 1912, ix, 206.

137. Biedl: Innere Sekretion, 1913, Ed. 2, Part 2, p. 344. Gigon: Ergebn. d. inn. Med. u. Kinderh., 1912, ix, 206, especially Zur Lehre von der Azidose, pp. 285-299. Magnus-Levy: Ergebn. d. inn. Med. u. Kinderh., 1908, i, 352.

138. There are various other interpretations of the exact way in which carbohydrate deficiency may result in ketogenesis (Gigon: Arch. f. d. ges. Physiol., 1911, cxI, 509), but the fact itself is firmly established.

139. Baer: Arch. f. exper. Path. u. Pharmakol., 1905-1906, liv.

140. For literature see Hammarsten and Mandel: Text-book of Physiological Chemistry, 1912, pp. 508-515. Gross: Deutsch. Arch. f. klin. Med., 1912, cviii, 106.

141. Sandmeyer: (Footnote 73). Pratt: (Footnote 10). Abelman: Ueber die Ausnutzung der Nährstoffe nach Pankreas-Exstirpation, u. s. w., Inaug. Diss., Dorpat, 1890, cited by Allen: Glycosuria and Diabetes, Boston, 1913. Rosenberg: Arch. f. d. ges. Physiol., 1898, lxx, 371. Lombroso: Arch. di fisiol., 1910, viii, 209.

142. Pratt, Lamson and Marks: Tr. Assn. Am. Phys., 1909, xxiv, 266. Pratt and Spooner: (Footnote 9). Allen: Glycosuria and Diabetes, Boston, 1913, p. 996.

143. Thus Masuyama and Schild: Ztschr. f. phys. u. diät. Therap., 1900, iii, 451. Salomon: Berl. klin. Wchnschr., 1902, xxxix, 45. Meyer, E.: Ztschr. f. exper. Path. u. Therap., 1906, iii, 58. Ehrmann: Ztschr. f. klin. Med., 1909, lxi, 319. With these and many other results, the negative findings of Gross have but little weight.

144. Minkowski: Berl. klin. Wchnschr., 1890, xxvii, 333; Arch. f. exper. Path. u. Pharmacol., 1908, lix, 395. Lombroso: Beitr. z. chem. Phys. u. Path., 1908, xi, 81; Ergebn. d. Physiol. (Ascher-Spiro), 1910, ix, 1, especially p. 11, Sammelreferat. Arch. di fisiol., 1910, viii, 209. Arch. di farm., 1910, ix, 446. Allard: (Footnote 81). Niemann: Ztschr. f. exper. Path. u. Therap., 1909, v, 466.

145. Abelmänn: (Footnote 141). Hédon and Ville: Arch. de physiol. norm. et path., 1897, xix, 606, 662. Gross: Deutsch. Arch. f. klin. Med., 1912, cviii, 106.

146. Levin: Arch. f. d. ges. Physiol., 1896, lxiii, 171. Hédon and Ville: (Footnote 145). Pratt and Spooner: (Footnote 9). Allen: Glycosuria and Diabetes, Boston, 1913, p. 996.

147. Minkowski: Berl. klin. Wchnschr., 1890, xxvii, 333. Lombroso: Beitr. z. chem. Phys. u. Path., 1908, xi, 81.

148. Lombroso: (Footnote 144). Brugsch: Ztschr. f. exper. Path. u. Therap., 1909, vi, 326.

149. Salomon: (Footnote 72). Ehrmann: Ztschr. f. klin. Med., 1909, lxi, 319. Pratt: (Footnote 10). Gross: Footnote 140.

150. Reach: Biochem. Ztschr., 1911, xxxiii, 436.

151. Concerning the relation of acidosis to hepatic insufficiency. see: Allard: (Footnote 81). Friedmann and Maase: Med. Klin., 1910, xxxi, 445. Blum: München. med. Wchnschr., 1910, lvii, 682. Neubauer: (Footnote 90).

152. A totally depancreatized dog has lost all ability to oxidize dextrose four days after the operation (Verzar and Fejer, Footnote 84).

153. Allen: Glycosuria and Diabetes, Boston, 1913.

154. Compare Mosenthal, E. Myer, Wegele. Allen himself admits this further on (Glycosuria and Diabetes, p. 815).

155. Pflüger: Arch. f. d. ges. Physiol., 1907, cxviii, 285: "Negative Beweise aber haben an sich keine entscheidende Kraft, wenn nicht der Beweis vorliegt, *warum* sie negativ sind."

156. "Ein negativer Erfolg kann durch verschiedene andere Gründe bedingt sein. So kann—um nur eine Möglichkeit zu erwähnen—die dem ganzen Körper aus dem das Pankreas-Hormon vollkommen verschwunden ist auf diese Weise zugeführte Menge immer noch zu klein sein, um eine zu Zuckerverbrennung genügende Konzentration zu erreichen." Pflüger, too, has admitted this (Arch. f. d. ges. Physiol., 1907, cxviii, 267).

157. Biedl: Innere Sekretion, 1913, Ed. 2, ii, 359: "Das gesamte Tatsachenmaterial über Pankreasdiabetes . . . spricht wohl entschieden dafür, dass hier bei ein inneres Sekret des Pankreas in Wegfall gekommen ist, welches de norma im Kohlenhydratstoffwechsel des Organismus eine ausschlaggebende Rolle spielt."

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Pflüger: *Arch. f. d. ges. Physiol.*, 1908, cxxiv, 633.  
Pratt, J.: *Am. Soc. Adv. Clin. Investig., Sec. Ana. Mt.*, May 2, 1910, p. 6, cited by Mosenthal (Footnote 76).  
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# STUDIES ON THE PATHOLOGICAL PHYSIOLOGY OF THE HEART

## I. THE INTRA-AURICULAR, INTRAVENTRICULAR AND AORTIC PRESSURE CURVES IN AURICULAR FIBRILLATIONS \*

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### INTRODUCTION: THE VALIDITY OF EXPERIMENTAL RESULTS IN THE INTERPRETATION OF CARDIAC AFFECTIONS

The experimental investigator who, within the span of at most a few hours, seeks to reproduce in animals the cardiac affections which Nature pleases to produce in man in a slow and gradual fashion, runs the risk of bringing about conditions which may not be comparable to those actually existing in diseased individuals. Thus, the sudden tearing of a valve may produce a reaction in experimental animals that is more serious than a similar insufficiency, the gradual development of which is accompanied by compensatory phenomena. It becomes a part of the experimental problem, therefore, not only to elucidate the dynamic effects of a certain pathological change, but also to determine, as completely as possible, the influence that secondary accompaniments to such a condition have on the primary affection.

Moreover, the hearts of animals on which experimental work is carried on are necessarily depressed by operation as well as anesthetic. Even if the anesthetic is wisely chosen and cautiously administered, shock and hemorrhage being reduced to a minimum, the very acts of opening the chest, instituting artificial respiration and removing the pericardium all operate to alter the pressure relations in the heart and large vessels so that the circulation can no longer be regarded as normal. Emphasis may, therefore, be laid on the fact that, in this series of investigations, the effort has been made to have, previous to the production of any pathological disturbance, an "effective auricular pressure" and an arterial pressure as nearly normal as possible. This was accomplished by giving the animal a very mild artificial respiration which caused an accumulation of carbon dioxide in the blood. Furthermore, the pericardium was retained in normal position in these experiments. If this procedure failed to restore normal pressure relations, an infusion of a saline containing 0.2 per cent. dextrose and a 1 : 10<sup>9</sup> concentration

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\* The first of a series of experimental and clinical investigations of pathological cardiac conditions made by means of optically recording instruments.

of epinephrin was allowed to enter the external vein very slowly but continuously.

A third difficulty in studying accurately the pressure changes during cardiac disturbances has recently been eliminated. It appears from the critical analysis of the static and dynamic requirements of recording apparatus by Frank<sup>1</sup> that, until recently, physiologists have not been supplied with apparatus which could accurately follow pressure changes in the cardiovascular system. The records obtained were but distorted images of what actually occurred. This unrecognized difficulty has

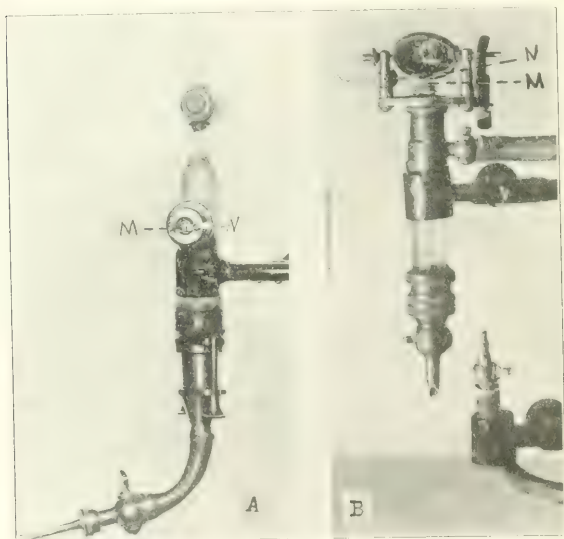


Fig. 1.—Two optically recording manometers: *A*, manometer for auricular, venous or arterial pressures; *B*, manometer for intraventricular pressures; *M*, movable mirror; *N*, calibrating mirror.

given a false feeling of finality in regard to data concerning phenomena involved in the normal as well as the pathological physiology of the circulation. Fortunately, however, it is now possible, on the principles worked out by Frank, to construct optically recording manometers whose efficiency exceeds the demands on them. Only such instruments have been utilized in these researches.

1. Frank: *Ztschr. f. Biol.*, 1903, xliv, 445; 1908, L, 309; 1910, liii, 429, 545; 1911, lv, 547.

## THE OPTICALLY RECORDING APPARATUS

1. *Manometers*.—The two types of optically recording manometers are shown in Figure 1. The instrument *B*, used to study intraventricular pressure, has been described in detail,<sup>2</sup> while the instrument *A*, used to study the venous, auricular and arterial pressure, resembles, in principle, another instrument which has also been described,<sup>3</sup> but differs in that it terminates below in a metal cannula which can be rotated and bent at different angles very much as the metal portion of Frank's spiegel-manometer.

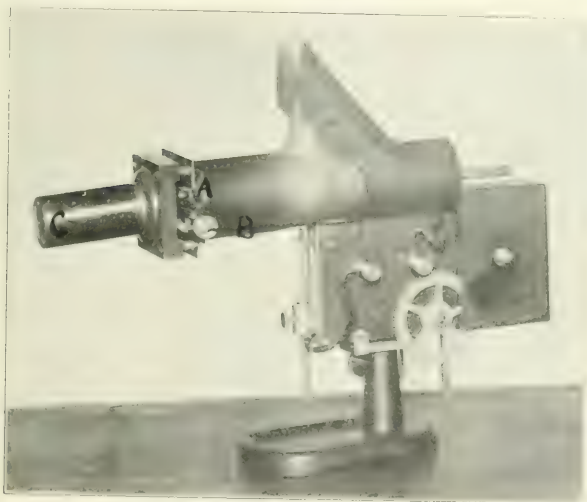


Fig. 2.—Arc light for producing a band of light of variable width. Description in text.

2. *Source of Illumination*.—A small 5-ampere lamp (E. Leitz & Co.), the carbons of which are automatically advanced by clockwork, provides a light of constant intensity (Fig. 2). The rays rendered parallel by a lens at the end of a light-proof hood at *A* pass through a slit the width of which can be regulated through a movable parallelogram system operated by a screw at *B*. By means of this system it is possible to adapt the width of the band to the extent of the excursion, a convenience appreciated when records of very different amplitude

2. Wiggers: Am. Jour. Physiol., 1914, xxxiii, 385.

3. Wiggers: Am. Jour. Physiol., 1914, xxxiii, 8.

need to be recorded.<sup>4</sup> The band of light is focused by a lens *C* on the small mirror of the instrument and reflected as a band of light to the photographic kymograph.

3. *Photokymograph*.—Instruments for obtaining long records have been devised by Edelman<sup>5</sup> and Frank.<sup>6</sup> Some personal experience with both of these photokymographs has led to a selection from each of them of features which, for my purpose, were most desirable, and to their incorporation with certain other features in a new photokymograph (Fig. 3). The fundamental mechanism used by Edelman to propel the paper is retained, except that the camera stands vertically

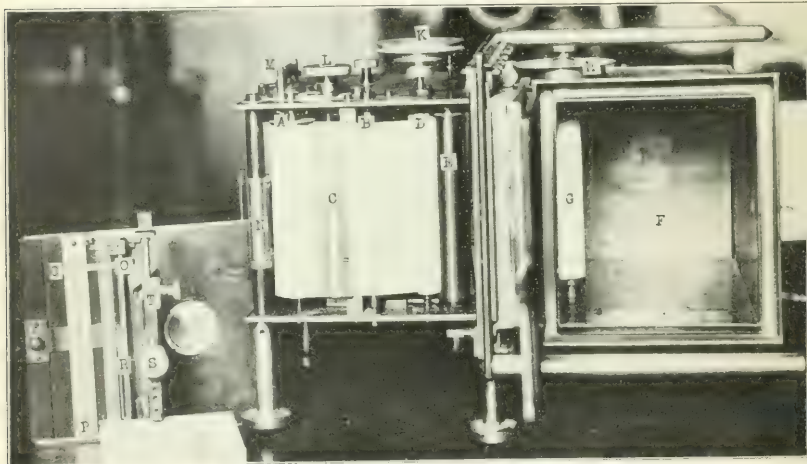


Fig. 3.—Photokymograph showing internal mechanism when front is removed and door of box *F* open. Description in text.

and all rollers move on conical pivots. The paper, 11.8 cm. wide, is fed from a roll 30 meters long and guided by two rollers, *A* and *B*, through a slot *C* and then made to pass between two rubber rollers *D* and *E*. The rubber roller *A* is moved at a definite speed by belting the pulley *K* with a motor and reducing gear. By rotating the knob *L*, the roller *E* is pressed against the roller *D* and the paper is drawn

4. For a discussion of this question see Garten: *Tigerstedt's Handbuch der physiologischen Methodik*, 1911, i, 100.

5. Edelman: Description in catalogue of Edelman Company, Munich.

6. Frank: Reported by Garten: *Tigerstedt's Handbuch der physiologischen Methodik*, i, 107.

through as by a wringer and passed through a slot into the box *F*. Here it is wound on a roller *G* by a spring attachment *H* as fast as it is fed into this box. This arrangement enables one to dispense with the enormous box of the Edelman apparatus, and is much simpler in construction than the complicated winding gear of Frank's apparatus. At *M* a meter indicating the amount of paper rolled off is introduced. This meter is actuated as follows: The roller *A* is 10 cm. in circumference. As the paper passes over the roller it is maintained in perfect contact by a smaller roller and weak spring at *N*. During every revolution of roller *A* (which occurs each time that 10 cm. of paper has passed) a single tooth at its top engages in one of ten teeth of a sprocket wheel on which a pointer indicates the number of centimeters on a dial. This sprocket likewise engages in a similar manner during every revolution with one of ten teeth of a second sprocket and its pointer indicates the number of meters on a second dial. In turning the knob *L*, the shutter is opened a short interval after the paper has begun to move. The band of light reflected from the mirror crosses the front of the camera as at *O-O'*. At *P* is a scale on which the band can be focused and the extent of its movement determined. A vertical section of this band of light is focused as a line on the paper at *C* by the cylindrical lens *R* on which a scale of 2 mm. is etched. As in Frank's photokymograph, a metal shade (*Y*, Fig. 4) prevents the light of an ordinary room from affecting the film unless the camera is faced toward a window.

Instead of photographing on the paper the numbers of experiments or date which are visible only after development, it is found more desirable when long records are taken, to punch into the paper a set of perforations corresponding in number to the number of the observation or experiment. This is accomplished by the device shown at *T* (Fig. 3), consisting (as shown in Figure 4 in its more lateral view) of a row of ten pointed rods (*X*), any number of which can be entered through the front of the camera by pushing the knob *S*. The rod *Q* controls the number of rods pushed in.

After the termination of an experiment, the paper is cut off by a knife pushed in from behind, which also closes the camera. The slit in the box *F* is likewise closed by pushing in a slide. The entire box containing the roll of exposed bromid paper is removed to a dark room where, with the guidance of the perforations, the roll can be cut into strips convenient for development. I am indebted to the laboratory mechanic, Mr. James Evenden, not only for working out many details of the kymograph, but for many new suggestions in the process of construction.

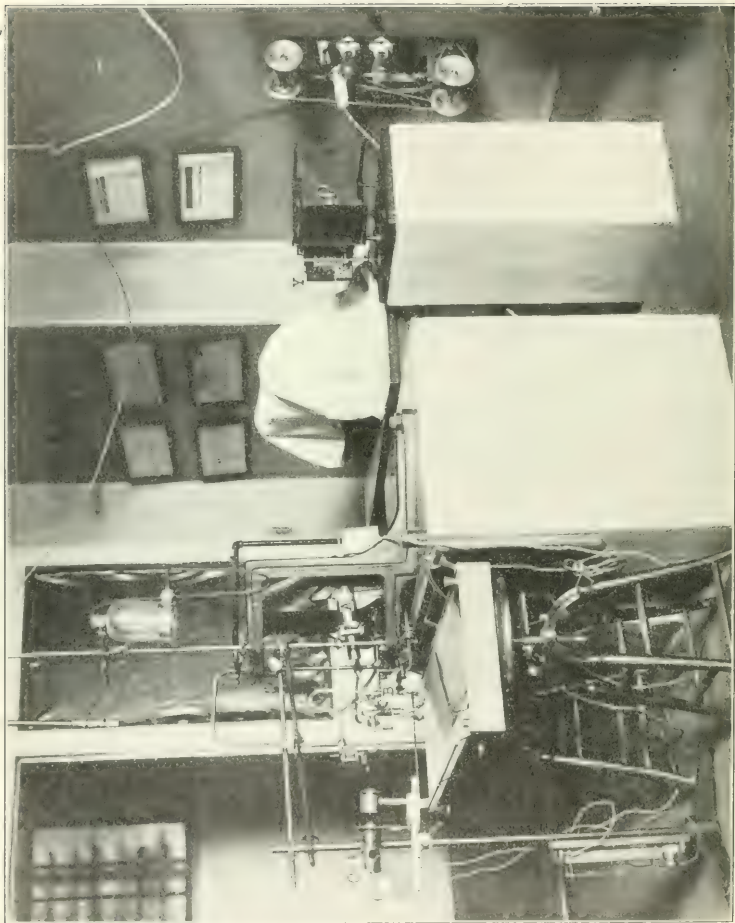


Fig. 4.—Photograph showing the mounting, alinement and adjustment of apparatus.



4. *Mounting and Alinement of Apparatus.*—The main features of the mounted apparatus and its relation to the animal board are evident without further description from the photograph of Figure 4. The band of light from the lamp *A*, set on the cement pillar, is focused on the small mirror of the upright manometer *B* and reflected to the photokymograph which is mounted on a separate pillar. The angle between incident and reflected rays is kept as small as possible. The band of light generated by the lamp *C*, mounted on an iron support clamped to the fixtures of the cement pillar, is focused on the mirror of manometer *E*, whence it is reflected through a small angle to the movable mirror *D*, and so a second time reflected to the optical camera. Since the mirrors of these optical manometers could not be placed exactly in the same vertical plane as the axis of the cylindrical lens, the section of the light bands entering the camera would be brought to a focus at slightly different places on the paper; hence it was necessary when accurate time relations had to be established to expose the paper briefly in the kymograph while stationary. As a rule, the correction was less than 1 mm. and for many purposes could be ignored.

#### THE NORMAL PRESSURE CURVES AND THEIR TIME RELATIONS

The normal pressure curves in the auricle, ventricle and carotid have been studied by optical manometers by Frank, Straub, Piper, Tigerstedt and myself. Although slight discrepancies exist in the curves obtained, it is possible to express the relations diagrammatically as judged by the combined work of all these investigators.<sup>7</sup>

*Aortic Pressure* (Plot I, Fig. 5).—Following the description given by Frank, the aortic pressure curve shows a more or less pronounced auricular wave (1, 2, 3), a preliminary vibration (3, 4, 5) synchronous with the isometric period of ventricular contraction, the primary shock (5, 6) due to the sudden ejection of blood with the arteries; the systolic summit reached at 7, the slow fall terminating in the incisure at 8 which marks the end of systole. After this the pressure slowly falls in diastole.

*Intraventricular Pressure.*—The curve in the two chambers does not differ in its essential features, although the top of the left ventricular curve (Plot II) is broader, that of the right (Plot III) being more rounded or even peaked. The auricular contraction causes a wave (1, 2, 3), which is followed, after several confused vibrations by a rise (3-5) during which the semilunar as well as the auriculoventricular valves are closed, and hence the heart contracts isometrically. After the opening of the valves, the rise continues for a brief interval

7. For reference see Wiggers: *Am. Jour. Physiol.*, 1914, xxxiii, 382.

and the intraventricular pressure responds by a slight though much damped oscillation to the primary rise 5, present in the arterial system. During the ejection period the contour corresponds to the top of the arterial curve since ventricle and arteries form a common cavity. The pressure continues to rise, and late in systole, reaches a summit (7), from which it gradually recedes to 8, where the beginning of relaxation causes a sharp drop of pressure to the base line. In the right ventricle (Plot III) the summit (7) is sooner reached and a more marked fall occurs during the ejection period to 8.

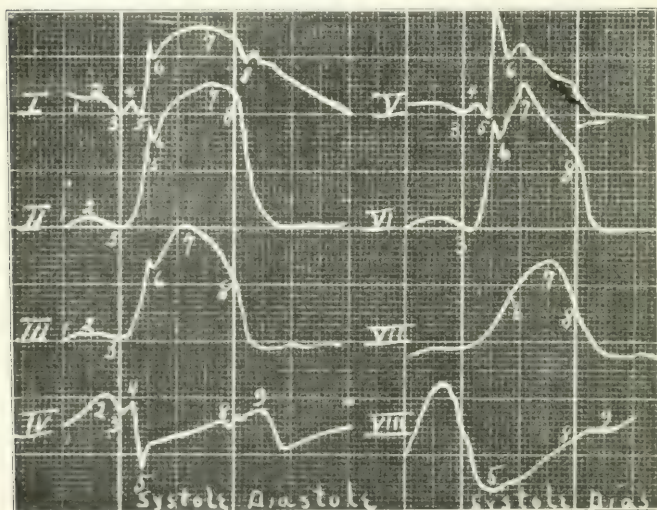


Fig. 5.—Plot showing semischematically the details of the pressure curves as determined by optically recording manometers: I, normal aortic pressure; II, normal left ventricular pressure; III, normal right ventricular pressure; IV, normal right auricular pressure; V, aortic pressure with low resistance; VI, left ventricular pressure with low resistance; VII, right ventricular pressure, low venous pressure; VIII, right auricular pressure, high venous pressure.

*Intra-Auricular Pressures.*—There is no material difference in the pressure waves of the two auricles (Plot IV, Fig. 5). Auricular systole causes the chief rise (1, 2) and diastole the first fall (2, 3). At the beginning of ventricular systole a short positive rise followed by a rapid negative drop of pressure occurs (3, 4, 5). It remains a question whether this represents more than a vibration of the auriculo-ven-

tricular valves, or whether, as is usually supposed, first a bulging of the auriculoventricular septum and later a downward movement occurs. Sometimes only a positive wave (3-4) occurs, at other times only the negative wave is present. Often no wave or oscillation of any kind appears. The factors that determine these variations are not established. During ventricular systole the pressure in the auricle rises because of a stasis. This rise continues unmarred except by an occasional vibration synchronous with the semilunar closure (8) until early diastole, when the auriculoventricular valves open and the auricular pressure falls. This does not occur until the ventricular pressure is very low (9).

*Atypical Curves.*—It may be pointed out that such typical curves are not uniformly obtained; *in fact, they are never obtained unless special precautions are taken to counteract the deleterious influences of anesthetic and operative procedures.* The chief variations encountered are due, in the aortic curve, to a low diastolic pressure; in the auricular curve, to a low or high effective venous pressure, and in the ventricular curves to the resultants of both of these influences. A low diastolic pressure in the arteries (Plot V) causes the primary oscillation 5-6 to become greater and more pronounced, while the systolic summit at 7 is much lower and the incisure occurs nearer to the diastolic pressure level. The left intraventricular pressure curve in such cases (Plot VI) resembles more the pressure curve in the right ventricle or acquires a peaked appearance because its maximum is rapidly reached.

The auricular pressure determines the gradient of the isometric rise, the curves becoming steeper with each increase in pressure. The contour of the ejection curve is also secondarily modified, as described in a recent contribution. A curve showing the type of intraventricular pressure curve when the venous pressure is low is shown in Plot VII.

In the auricular curve the chief differences consist in the entire absence of the systolic vibrations already mentioned and a more rapid and complete rise of pressure during systole (Plot VIII). Occasionally, the pressure fails to fall materially at the opening of the tricuspid valves. The size of the auricular wave varies exceedingly.

#### THE PRESSURE CURVES IN AURICULAR FIBRILLATION

The characteristic pressure variations produced during experimental auricular fibrillation are best analyzed by reference to a number of records taken from seven experiments on the subject.

In Figure 6 are shown simultaneous records of the subclavian (upper) and left auricular pressures (lower). The short record at A indicates the nature of the normal pressure curve just before the onset of fibrillation. In Record B is shown by contrast the effect of auricular

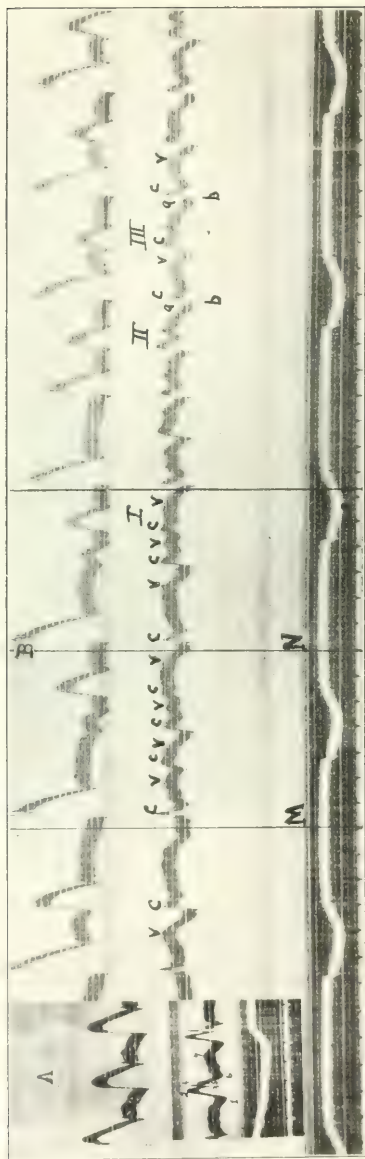


Fig. 6.—Synchronous records of the subclavian pressure (upper record) and the right auricular pressure (middle record). Lower record, artificial respiration. Record A: Normal pressures; 1, 2, 3, auricular wave; 3, 4, 5, early systolic fall of pressure. Record B: Pressure after auricular fibrillation, showing absence of auricular waves, retention of characteristic vibrations, *a*, *b*, *c*, during strong systoles of ventricle. Various other types of waves in weak systoles—described in text.

fibrillation. In the intra-auricular curve there is an entire absence of an auricular wave such as is shown at 1, 2, 3 in the normal curve (*A*). Strong ventricular contractions are initiated by a sharp negative depression (*a-b*) followed by a sharp positive wave (*b-c*) as in the normal pulse. Weaker ventricular systoles, such as are marked I, II, III in the subclavian pulse, cause no such sharp valvular vibrations. They may, as in Wave I, produce merely a ripple in the intra-auricular curve, or after a negative depression (*a-b*) cause a wave which is either sharp as in Wave II or rounded as in Wave III.

During diastole the pressure falls at V, which to judge from the interval after the closure of the semilunars is due, as in the normal pulse, to the opening of the tricuspid valves. In addition to the early systolic oscillations (*a, b, c,*) and the diastolic fall (*v*), there occur other waves of shorter duration. These waves were obtained in experiments in which careful observation failed to reveal any coordinated auricular contraction, and hence they cannot be attributed to attempts at coordinated auricular contractions. There is also no proof that the resultant effect of fibrillary contractions can create wavelets of as long duration as these. When, at the end of experiments, the ventricle has entirely stopped and the still beating auricles are thrown in fibrillation, no waves are produced in the auricular pressure curves. It seems probable, therefore, that they are related to ventricular events not recorded in the arterial waves. Evidence that this is the case is presented later on in the paper. According to this interpretation, the period between the lines *M N* contains not two ventricular systoles as indicated by the subclavian pulse, but probably four systoles, each of which causes a *c-v* wave-group in the auricular pressure curve.

The pressure changes which occur within the left ventricle during auricular fibrillation are shown in Figure 7, synchronous with the subclavian pressure curves. The isometric period (*Anspannungszeit*), as shown in Wave 2, extends from *A* to *B*, the ejection period from *B* to *C*. It is evident that systoles varying greatly in strength occur without definite order during auricular fibrillation. The differences in the systoles of different strength manifest themselves in the gradient of the upstroke, in the contour of the ejection period and in the slope of the relaxation curve.<sup>8</sup> It is obvious that the variations in the gradient of the upstroke and ejection period do not, as in hearts in which a normal rhythm exists, depend on the initial tension,<sup>8</sup> but rather on the interval between its onset and the end of the previous contraction. The waves occurring the shortest interval after systole are smallest and the rise is more gradual. According to this view, the waves num-

8. For further details compare Wiggers: Am. Jour. Physiol., 1914. xxxiii. 382



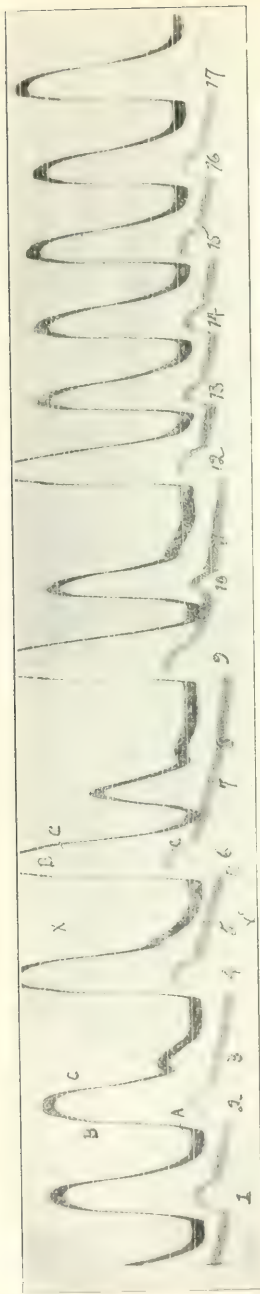


Fig. 7.—Synchronous records of left ventricular (upper) and subclavian pressures (lower) during auricular fibrillation. Description in text.

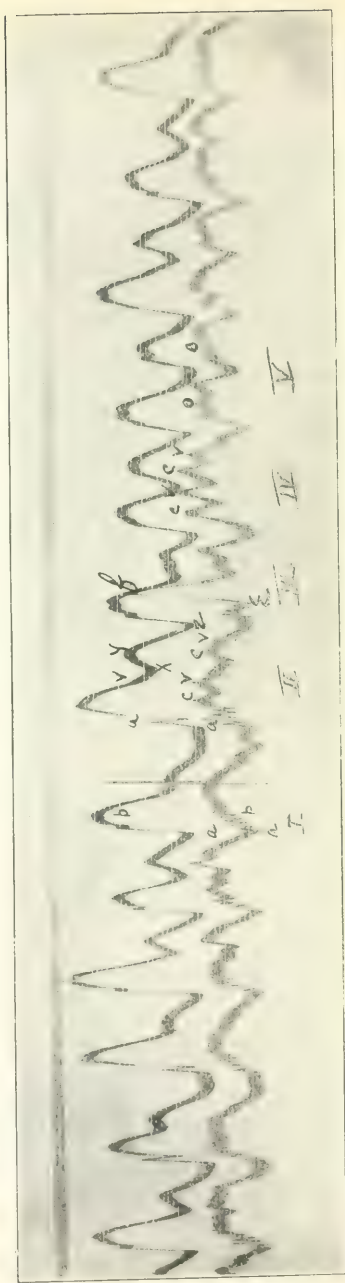


Fig. 8.—Synchronous record of right ventricular and right auricular pressures showing effect of tricuspid regurgitation and effect of weak ventricular systoles on right auricular pressure. Details described in text.



bered 5, 3, 7, 10, 2 and 9 may be arranged as a series. When, however, an extra supply of energy is exhausted by two rapidly recurring systoles, the third wave (as at 8 and 11) may be very small even though a longer interval intervened. The rate of relaxation is directly related to the strength of systole; partly, at least, because, in the weaker systoles, less blood is ejected, partly also, perhaps, because the inherent rate of muscular relaxation is slower, although no direct evidence for this is obtained (cf. e. g., Waves 7, 2 and 6).

The pressure of an aortic pulse curve as well as its shape depends to some extent on the strength of the ventricular systole, but is also governed by the height of the diastolic pressure at the end of the isometric period of cardiac contraction. Thus, while the gradient of the ventricular upstroke and the height of the curve in Waves 10, 13 and 15 are not materially different, the size and shape of the corresponding arterial curves vary extensively. When the semilunar valves fail to open as in Wave 7, the second heart sound fails to occur, while in weaker contractions such as 3, 8 and 11, no sounds can be heard by a stethoscope applied to the dog's heart. This is worthy of note in estimating the "pulse deficit" by auscultating for the heart sounds in auricular fibrillation.

The previous records illustrate a class of cases of auricular fibrillation in which the rhythm given by the ventricle, though irregular, carries on the circulation in a fairly normal fashion. In the experiment shown in Figure 7 the mean pressure in the arteries ranged around 90, and no auricular engorgement or tricuspid regurgitation occurred. Quite a different picture is given, however, by another class of experiments in which the efficiency of the ventricle is impaired. In Figure 8 is shown a section of a record from a case in which the heart was dilated, the venous pressure high and the carotid mean pressure averaged 27 mm. Each group of waves in a heart cycle becomes an interesting study of its own. In Group I, it is shown that the ventricle is still capable of giving strong beats. The intraventricular curve appears fairly normal in spite of some regurgitation, which is made evident in the auricular curve both by the sudden rise of pressure during ventricular systole and by the murmur vibrations created at *a*. In Group II, a vibration occurs in the ventricle, which corresponds exactly in time with the first vibration in the auricle. Little regurgitation probably occurred in this beat. In the auricles are produced a distinct *c* and *v* wave. During the attenuated systole, *x y z* waves corresponding to a *c* rise and a *v* fall are present. Without an intraventricular pressure curve as a guide, these waves might be interpreted as occurring during the diastole of the previous beat or cycle. The third wave group shows after a valvular vibration and at the beginning of

the ejection period a sudden rise *e, f*, apparently indicating that the tricuspid valves were suddenly rendered incompetent during the height of the ejection period and permitted a sharp regurgitation. In the fourth group marked out, two weak ventricular systoles cause no regurgitation, but produce a series of four distinct waves comparable to the *c* and *v* waves explained in Figure 6. Similar ventricular contractions are, however, accompanied by a regurgitation. This occurs in the two waves of Group V, as shown by the immediate and sustained increase of pressure in the auricle as well as by the murmur vibration superimposed at *o*. The chief deviation of the intraventricular pressure curve consists in the slow rate of relaxation which might result from a high degree of tonus or be due to a great accumulation of blood within the ventricle because the average systole occurs with too little vigor. Since the vigor of the systole is inversely related to the frequency of the ventricular contraction, it is apparent that the most efficient circulation will be maintained in auricular fibrillation when the beats are initiated somewhat slowly. Undoubtedly, the well-known beneficial influence due to digitalis in such cases is due to this fact.

#### SUMMARY

The details of the pressure changes in the auricles, ventricles and aorta during auricular fibrillation were studied by means of optically recording manometers of high vibration frequency.

*Intra-Auricular Curve.*—In experimental animals the fibrillating contractions in the auricle in themselves produce no intra-auricular pressure waves. The strong ventricular contractions cause a sharp oscillation in the auricle during early systole, while weaker contractions often cause a single rounded wave or a double oscillation similar to *c* and *v* waves of the normal pulse. When, as often happens, two or three weak contractions which produce no pulse in the arterial system follow each other, a series of small waves are created in the auricle (two to each ventricular systole) which gives the erroneous impression that they occur during ventricular diastole.

*Intraventricular Pressure Curve.*—The intraventricular pressure curves show that the ventricle contracts at a very irregular rate. The height of the pressure and the gradient of the isometric rise before the semilunar valves open is determined largely by the interval between contractions. Hence, whenever the pace is set too rapidly a series of inefficient systoles results which may cause the arterial pressure to fall and the ventricle to dilate. As these weaker contractions often begin before the *a-v* valves are open and are not strong enough to open the semilunar valves, it follows that such contractions may be accompanied

by no audible sound. It is important to realize this clinically in estimating the ventricular rate by auscultation in such cases.

*Central Arterial Pulse.*—Since the aortic pressure is affected only by those systoles which elevate intraventricular pressure above the arterial diastolic pressure, it follows that the contour and amplitude of the arterial waves depends not only on the strength of ventricular contraction, but on the diastolic pressure as well. Since the venous pulse tracings taken from the supraclavicular region are always complicated by arterial impacts from the central arteries, the failure to recognize this may lead to misinterpretation of the systolic wave groups. The failure to recognize that the arterial pulse amplitude is not a criterion of the strength of the heart-beat in such cases has given rise to the erroneous impression that the strength of the ventricular systoles follows no law, whereas the intraventricular pressure curves show that the vigor of ventricular systole is largely governed by the time relations between contractions.

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## THE DISTRIBUTION OF IODIN IN THE CELL FOLLOWING ADMINISTRATION OF ORGANIC IODIN PREPARATIONS \*

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In a previous communication<sup>1</sup> results of analyses of tissues were given, showing essential differences in the distribution of iodine in the various constituents of the cell after administration of different iodine preparations. It was believed that a further series of analyses might serve to confirm these results, and throw light on the fate of various organic iodine preparations in the body. It had been previously shown by other investigators that after administration of iodized fats a larger relative proportion of iodine was found in the organs rich in lipoids, such as the brain, spinal cord and liver. Their results had been taken to show that these iodized fats were absorbed in a lipoid soluble form, and were held by the lipoids in the cells. This being the case, these substances should produce a relatively larger amount of iodine in the lipoid fraction, after extraction and separation of the tissue elements according to Koch's method.<sup>2</sup>

In order to establish the results, it was necessary to demonstrate that after mixing various iodine preparations with liver tissue, the tissue originally chosen for the experiments, these substances would follow their solubilities during the extraction process. By a comparison of the results of analyses following mixture of the substances with liver tissue, and analyses of liver following administration of the preparations to live animals by different methods, some idea has been obtained as to the changes in these substances during the process of absorption.

The experiments were carried out in practically the same manner as those previously reported. Extraction of the lipoids, separation of the water-soluble constituents, etc., was done by the method of Koch.

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\* From the Laboratory of Pharmacology, University of Oregon, Department of Medicine.

\* Investigation supported in part by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

1. McLean, Franklin C.: Organic Iodine Preparations, Their Pharmacology and Therapeutic Value, *THE ARCHIVES INT. MED.*, 1912, x, 505.

2. Koch, W.: *Jour. Am. Chem. Soc.*, 1909, xxxi, 1330.

All iodine determinations were made by the method described by Hunter,<sup>3</sup> with the slight modifications suggested by F. C. Koch.<sup>4</sup>

The following protocols and accompanying tabulation show the results of the experiments made. For the sake of completeness, the results of the four experiments heretofore reported are included, as Series A.

## EXPERIMENTS WITH POTASSIUM IODID

EXPERIMENT V.—Feb. 4, 1914, 20 gm. liver mixed with 5.2 mg. potassium iodid and put in alcohol immediately.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid .....	.071	34.1
Water-soluble, alcohol-soluble....	.137	65.8
	<hr/> .	
	.208	

EXPERIMENT VI.—Feb. 4, 1914, 20 gm. liver mixed with 5.2 mg. potassium iodid and allowed to stand one hour at room temperature before mixing with alcohol.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid .....	.0761	32.3
Water-soluble, alcohol-soluble....	.159	67.6
	<hr/> .	
	.2351	

EXPERIMENT IX.—Rabbit 2,000 gm.

April 6, 1914, 0.3 gm. potassium iodid subcutaneously.

April 7, 0.3 gm. subcutaneously.

April 8, 0.3 gm. subcutaneously, 9:30 a. m.

Killed by bleeding 5 p. m.; weight of liver 54 gm. Liver showed marked fatty changes; 20 gm. of liver taken for analysis.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid .....	.0697	30.5
Water-soluble, alcohol-soluble....	.1586	69.4
	<hr/> .	
	.2283	

EXPERIMENT V-A.—Rabbit, 1,600 gm.

July 22, 3 p. m., 0.8 gm. potassium iodid in water by stomach tube.

July 23, 9 a. m., 0.5 gm. potassium iodid in water by stomach tube.

July 23, 10:30 a. m., killed by bleeding from neck. Weight of liver 65.95 gm.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid (alcohol-soluble, water-in- soluble) .....	.032	32.0
Alcohol-soluble, water-soluble....	.067	67.0
	<hr/> .	
	.099	

3. Hunter: Jour. Biol. Chem., 1910, vii, 321.

4. Koch, F. C.: Jour. Biol. Chem., 1913, xiv, 101.

## EXPERIMENTS WITH IODALBIN

EXPERIMENT I.—Feb. 4, 1914, 20 gm. liver mixed with 20 mg. iodalbin, and allowed to stand one hour at room temperature before mixing with alcohol.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.0362	42.1
Lipoid (alcohol-soluble, water-in-soluble) .....	.0179	20.8
Alcohol-soluble, water-soluble....	.0317	36.9
	<hr/> 0.858	

EXPERIMENT II.—Feb. 4, 1914, 20 gm. liver mixed with 20 mg. iodalbin and put in alcohol immediately.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.0558	45.1
Lipoid .....	.0412	33.3
Water-soluble, alcohol-soluble....	.0267	21.5
	<hr/> .1237	

EXPERIMENT VI-A.—Rabbit, 1,600 gm.

July 25, 3 p. m., 2 gm. iodalbin in sodium bicarbonate solution by stomach tube.

July 26, 11:45 a. m., 2 gm. iodalbin in sodium bicarbonate solution by stomach tube.

July 26, 2 p. m., killed by bleeding from neck. Weight of liver, 70.45 gm.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	0.000	00.0
Lipoid (alcohol-soluble, water-in-soluble) .....	.014	24.5
Alcohol-soluble, water-soluble....	.043	75.4
	<hr/> .057	

## EXPERIMENTS WITH SAJODIN

EXPERIMENT III.—Feb. 4, 1914, 20 gm. liver mixed with 26 mg. sajodin and put in alcohol immediately.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid .....	.111	89.8
Water-soluble, alcohol-soluble....	.0126	10.1
	<hr/> .1236	

EXPERIMENT IV.—Feb. 4, 1914, 20 gm. liver mixed with 16 mg. sajodin and allowed to stand for one hour at room temperature before mixing with alcohol.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid .....	.072	83.0
Water-soluble, alcohol-soluble....	.023	16.9
	<hr/> .195	

EXPERIMENT II-A.—Rabbit, 1,790 gm.

June 24, 0.3 gm. sajodin in olive oil subcutaneously.

June 25, 0.3 gm. sajodin in olive oil subcutaneously.



June 26, 9:30 a. m., 0.5 gm. sajodin in olive oil subcutaneously.

June 26, 1:30 p. m., killed by bleeding from neck. Weight of liver 54.9 gm.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid (alcohol-soluble, water-in- soluble) .....	.0106	62.7
Alcohol-soluble, water-soluble....	.0063	37.3
	<hr/> .0169	

EXPERIMENT IV-A.—Rabbit, 1,400 gm.

July 17, 2:10 p. m., 2 gm. sajodin in alcohol by stomach tub

July 18, 9:30 a. m., 2 gm. sajodin in alcohol by stomach tube.

July 18, 1:30 p. m., killed by bleeding from neck. Weight of liver 49.5 gm.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.010	6.4
Lipoid (alcohol-soluble, water-in- soluble) .....	.082	52.9
Alcohol-soluble, water-soluble....	.063	40.6
	<hr/> .155	

#### EXPERIMENTS WITH IODIPIN

EXPERIMENT VIII.—Rabbit, 2,950 gm.

Feb. 18, 1914, given 7.3 c.c. iodipin (10 per cent.) subcutaneously.

February 19, 7.3 c.c. subcutaneously.

February 20, 7.3 c.c. subcutaneously.

February 21, 7.3 c.c. subcutaneously, 10 a. m.; 2 p. m., killed by bleeding; weight of liver 100 gm.; 20 gm. of liver taken for analysis.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid .....	.0052	55.9
Water-soluble, alcohol-soluble....	.0041	44.0
	<hr/> .0093	

EXPERIMENT VII.—Rabbit, 3,400 gm.

Feb. 18, 1914, given 8.5 c.c. iodipin (10 per cent.) by stomach tube.

February 19, 8.5 c.c. rectally.

February 20, 8.5 c.c. rectally.

February 21, 8.5 c.c. rectally, 10 a. m.; 2 p. m., killed by bleeding; weight of liver 82 gm.; 20 gm. of liver taken for analysis.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid .....	.0359	77.3
Water-soluble, alcohol-soluble....	.0105	22.6
	<hr/> .0464	

#### EXPERIMENTS WITH IODIVAL

EXPERIMENT XI.—Rabbit, 2,000 gm.

April 6, 1914, 1 gm. iodival subcutaneously, with alcohol.

April 7, 1 gm. subcutaneously.

April 8, 1 gm. subcutaneously, 9:30 a. m.; 5:30 p. m., killed by bleeding; weight of liver 69 gm.; 20 gm. of liver taken for analysis.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid .....	.0190	81.8
Water-soluble, alcohol-soluble....	.0042	18.1
	<hr/> .0232	

EXPERIMENT XII.—Rabbit, 2,000 gm.

April 6, 1914, 1 gm. iodival subcutaneously, with alcohol.

April 7, 1 gm. subcutaneously.

April 8, 1 gm. subcutaneously, 9:30 a. m.; 5:30 p. m., killed by bleeding; weight of liver 77 gm.

<i>Analysis:</i>	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue .....	.000	00.0
Lipoid .....	.0126	75.0
Water-soluble, alcohol-soluble....	.0042	25.0
	.0168	

TABULATION OF RESULTS OF EXPERIMENTS			Per Cent. I in Water- Soluble, Alcohol- Soluble
	Per Cent. I in Protein Res.	Per Cent. I in Lipoid	
<i>Potassium Iodid:</i>			
V Mixed with tissue.....	00.0	34.1	65.8
VI Mixed with tissue.....	00.0	32.3	67.6
IX Subcutaneous .....	00.0	30.5	69.4
V-A By stomach .....	00.0	32.0	67.0
<i>Iodalbin:</i>			
I Mixed with tissue.....	42.1	20.8	36.9
II Mixed with tissue.....	45.1	33.3	21.5
VI-A By stomach .....	00.0	24.5	75.4
<i>Sajodin:</i>			
III Mixed with tissue.....	00.0	89.8	10.1
IV Mixed with tissue.....	00.0	83.0	16.9
II-A Subcutaneously .....	00.0	62.7	37.3
IV-A By stomach .....	6.4	52.9	40.6
<i>Iodipin:</i>			
VIII Subcutaneously .....	00.0	55.9	44.0
VII By rectum .....	00.0	77.3	22.6
<i>Iodival:</i>			
XI Subcutaneously .....	00.0	81.8	18.1
XII Subcutaneously .....	00.0	75.0	25.0

It will be seen that the distribution of iodine after potassium iodide is remarkably constant, whether the substance be mixed directly with the tissue, or administered subcutaneously or by the gastro-intestinal tract. The distribution of potassium iodide serves, therefore, as a comparison, as only one-third of the iodine remains with the lipid fraction during the process of separation of the fractions. The iodine products of fatty acids, however, show a marked increase in the iodine of the lipid fraction. As is to be expected, this lipid distribution is the greatest when the substance is mixed directly with the tissue, as no opportunity is offered for the splitting of the combination. In every case of administration of an iodine product of a fatty acid by whatever method there is a decided increase in the relative amount of the iodine of the lipid fraction. In the case of iodalbin the results were exactly what were to be expected. We had previously shown<sup>1</sup> that much of the iodine of iodalbin was in very loose combination with the protein, while some seemed to be more firmly bound. Extraction by the Koch

method left from 42 to 45 per cent. of the iodine recovered with the protein fraction, the remainder being practically evenly distributed between the two other fractions. When the substance was given by mouth it was apparently all absorbed in a water-soluble form, as none of it was left in the protein residue. This does not, of course, exclude the possibility of some of it being absorbed as an iodine product of an amino-acid.

The foregoing results apparently establish the *Lipotropic* theory of Loeb,<sup>5</sup> and demonstrate beyond a doubt that the iodized fatty acids are absorbed in a lipid-soluble form and are taken up by the lipoids of the cells. The greater amount of iodine found in the brain and other lipid-rich tissues by Loeb is thus explained. These iodized fatty acids may, as suggested by Meyer and Gottlieb,<sup>6</sup> circulate in the body as indifferent or inactive substances, be deposited in indifferent locations, and give off free iodine and allow it to act wherever the necessary conditions are present. This also explains the relatively more even excretion of these substances.

#### CONCLUSIONS

The method used is suitable for comparing the distribution of iodine in the cell after administration of various preparations.

The iodine derivatives of fats and fatty acids are absorbed in a lipid-soluble form after administration by the gastro-intestinal tract or subcutaneously, and are taken up and held in part by the lipoids of the cells.

Iodalbumin loses its identity during the process of absorption, and its iodine appears in the tissues entirely in water- or alcohol-soluble combination.

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5. Loeb: Arch. f. exper. Pathol., 1907, lvi, 310.

6. Meyer and Gottlieb: Pharmacologie, Berlin, 1911, p. 358.

STATISTICS OF PELLAGRA IN SPARTANBURG COUNTY,  
S. C., INCLUDING GEOGRAPHICAL DISTRIBUTION  
OF THE DISEASE AND ITS RELATION TO  
RACE, AGE, SEX AND OCCUPATION \*

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GEOGRAPHICAL DISTRIBUTION AND RACIAL DISTRIBUTION OF PELLAGRA  
IN SPARTANBURG COUNTY

The geographical distribution of pellagra in Spartanburg County was considered in detail in the First Progress Report.<sup>1</sup> In general, it was found that morbidity tended to vary directly with congestion of population, although this relationship was markedly disturbed by other factors. The villages of the cotton mills showed the highest morbidity and, when their population was excluded from the figures, the morbidity rate for the city dwellers was about the same as in the neighboring rural population, although somewhat above the morbidity of the rural population of the county as a whole.

The cases of pellagra in Spartanburg County on our records at the end of 1912 included 257 white persons and twenty-five colored (negro and mixed blood), representing a morbidity of 45 per 10,000 whites and 9.5 per 10,000 colored population. This difference was not regarded necessarily as evidence of racial resistance to pellagra on the part of the negro population, but it was thought that industrial conditions might account for it to a large extent.<sup>2</sup>

The field work of 1913 has added to our records of the number of cases in Spartanburg County, bringing the total number of recorded pellagrins up to 847. In 780 of the cases we know the race of the patient and the place in which he lived at the time the disease was recognized. Of these, 680 were white and 100 colored. We have obtained from the Census Bureau of the United States Department of Commerce and Labor, racial statistics of the population of the minor civil divisions of Spartanburg County. Our data enable us, therefore, to inquire into the total morbidity and the racial morbidity from pellagra, not only in the county as a whole, but also in each of these various minor civil divisions, which present differences in industrial and living conditions. The data are presented in Table 1.

\* Submitted for publication July 18, 1914.

\* From the Division of Tropical Medicine, Department of the Laboratories, New York Post-Graduate Medical School and Hospital.

1. Siler, J. F., and Garrison, P. E.: *Am. Jour. Med. Sc.*, 1913, cxlvi, No. 7, 46; First Progress Report, p. 21.

2. Siler, J. F., and Garrison, P. E.: *Am. Jour. Med. Sc.*, 1913, cxlvi, 51; First Progress Report, p. 26.

The general geographical distribution of the total 780 cases of Table 1 is not significantly different from that shown by the work of the previous year. The highest morbidity was found in the township of Spartanburg and it was somewhat higher (182 per 10,000) in the population of this township outside the city of Spartanburg proper than within the city limits (153 per 10,000). The only other township with a morbidity approaching these figures was Township E, 127 per 10,000, in which a large portion of the population lived in one mill-village. The townships devoted more especially to agriculture showed relatively much lower morbidity rates. It is probable that we have obtained somewhat less complete records of the actual cases existing in the rural districts, but we do not believe that this can account for the marked difference shown. Pellagra in the farming sections showed a distinct tendency to occur in definite foci of limited extent, in which a considerable proportion of the population was affected. In some of these foci the pellagra morbidity approached the figures observed in villages, but on the whole the rural pellagra morbidity was relatively low. We are compelled to believe that the population of the city and of the villages was, in the aggregate, much more subject to pellagra than the population of the country districts. In other words, higher pellagra morbidity was correlated with congestion of the population.

Within the city of Spartanburg, one small ward was practically free from pellagra, namely, Ward 3. The disease was most prevalent in the unsewered wards, 5 and 6, inhabited largely by the families of mill workers. The population of Spartanburg township outside of the city limits also showed a relatively high pellagra morbidity, 182 per 10,000. This population included the inhabitants of several mill-villages, together with a considerable agricultural population.

In all the townships the pellagra morbidity in the white population was considerably greater than in the colored. This was probably due in part to the fact that negroes were not employed in the cotton-mills and relatively few of this race lived in the mill-villages where the disease was most prevalent. It is also probable that our records of negro pellagrins are somewhat less complete than for pellagrins of the white race, although we do not believe that the discrepancy is very great. In general, it may be said that the negro population was more widely scattered than the white, being less than half as numerous in the first place and living for the most part on farms, except the 6,873 in Spartanburg city. In the principal negro section of the city, in Ward 1, the negro population was nearly equal in numbers to the white and in this ward the pellagra morbidity of the two races was approximately equal, 123 and 121 per 10,000. The financial status and general sanitary surroundings of the white people in this ward were on the average much better than for the negroes. The latter race lived in

TABLE 1.—PELLAGRA MORBIDITY OF WHITES AND NEGROES IN THE TOWNSHIPS OF SPARTANBURG COUNTY

Township	White			Negro			Total		
	Popula- tion	Pella- grin	Morbid- ity per 10,000	Popula- tion	Pella- grin	Morbid- ity per 10,000	Popula- tion	Pella- grin	Morbid- ity per 10,000
A. Campobello .....	6,587	23	35	2,092	4	19	8,679	27	31
B. Cherokee .....	4,147	29	70	1,103	1	9	5,250	30	57
C. Beech Springs.....	8,359	64	77	3,714	3	8	12,073	67	55
D. Spartanburg .....	21,143	448	212	10,208	72	71	31,354	520	166
E. Pacolet .....	3,576	62	173	1,921	8	42	5,501	70	127
F. Reidville .....	4,562	31	68	2,312	10	43	6,874	41	60
G. Walnut Grove.....	1,123	2	18	1,315	1	8	2,443	3	12
H. Glenn Springs.....	1,768	2	11	1,176	0	0	2,944	2	7
I. Woodruff .....	2,982	6	20	1,398	0	0	4,380	6	14
J. Cross Anchor.....	2,796	13	46	1,171	1	9	3,967	14	35
Total.....	57,048	680	119	26,410	100	38	83,465	780	93

TABLE 2.—PELLAGRA MORBIDITY OF WHITES AND NEGROES IN THE MINOR DIVISIONS OF SPARTANBURG TOWNSHIP

Locality	White			Negro			Total		
	Popula- tion	Pella- grin	Morbid- ity per 10,000	Popula- tion	Pella- grin	Morbid- ity per 10,000	Popula- tion	Pella- grin	Morbid- ity per 10,000
Ward 1.....	2,476	30	121	2,366	29	123	4,843	59	122
Ward 2.....	1,380	20	145	451	4	89	1,831	24	131
Ward 3.....	445	1	22	64	0	0	509	1	20
Ward 4.....	2,450	34	139	1,972	13	66	4,424	47	106
Ward 5.....	973	33	330	540	4	74	1,513	37	245
Ward 6.....	2,917	86	295	1,480	14	95	4,397	100	227
Total for city of Spar- tanburg .....	10,641	204	192	6,873	64	93	17,517	268	153
Township, excluding the city .....	10,502	244	232	3,335	8	24	13,837	252	182
Township, total.....	21,143	448	212	10,208	72	71	31,354	520	166



a wholly unsewered section in poorly constructed dwellings, while many of the white residents of this ward were of the well-to-do class living in well appointed homes. It would appear that the negroes in Spartanburg County have, as a race, been somewhat less subject to the disease than the white population. The difference is not sharp enough to warrant the belief in a distinct racial immunity of negroes, and it doubtless depends to a considerable extent on living conditions.

The smaller number of negroes present and the fairly complete social segregation of the races rendered association of negroes with pellagrins comparatively much less common. The negroes associated hardly at all with the white mill-village population and their closest social relation with the white race was doubtless in the capacity of household servants in the more well-to-do white families.

So many undetermined factors enter into the relationship that it seems unwise at this time to draw any very definite conclusions in regard to racial resistance to pellagra. We are inclined to believe that negroes as a race are only slightly, if at all, less susceptible to pellagra than the white population, and that the racial difference shown in our statistics for Spartanburg County is dependent to a large extent on the influence of other factors.

*Synopsis.*—The geographical distribution of pellagra in Spartanburg County has been very uneven, the morbidity being much higher in those townships in which the larger centers of population were situated and especially in the industrial communities surrounding the cotton-mills.

The disease was about three times more prevalent in the white population as a whole than in the negroes, but this ratio is not considered to be a true measure of the relative racial resistance to pellagra, but rather as the end-result of the influence of several factors, in part undetermined.

#### THE DISTRIBUTION OF PELLAGRA ACCORDING TO AGE AND SEX

The distribution of pellagra in respect to age and sex was discussed in the First Progress Report,<sup>3</sup> in which 282 cases then on our records were studied from this standpoint and compared with similar compilations of other published data. At the end of our field work in 1913, we have been able to compile data in regard to the age and sex of 740 cases in Spartanburg County, out of the total 847 cases of which we were able to obtain records, and it seems probable that these 740 cases represent a much larger proportion of all the cases which have actually occurred in this county than has been previously obtained in a unit population of comparable size. Further than this, we possess approximately complete data concerning the age and sex of 257 pellagrins

3. Siler, J. F., and Garrison, P. E.: *Am. Jour. Med. Sc.*, 1913, cxlvi, 44; First Progress Report, p. 31.

living in seven cotton-mill villages, six in Spartanburg County and one in Union County, S. C., which were studied by house-to-house canvass. In these villages we learned the age and sex of 131 pellagra patients in whom the first attack occurred in either 1912 or 1913, and this figure would seem to represent nearly the total number of cases incident there in these two years. Further, the complete census data on the population of these villages are available in our records. The opportunity is thus presented for a more satisfactory study of the distribution of pellagra according to age and sex than has been possible heretofore.

*Pellagra Morbidity in Spartanburg County.*—Of the 740 available cases in the county, 528 were females and 212 were males, a ratio of nearly  $2\frac{1}{2}$  to 1. For the present study it has not seemed worth while to consider the age of these individuals at the time the disease origi-

TABLE 3.—DISTRIBUTION OF PELLAGRA IN SPARTANBURG COUNTY ACCORDING TO AGE BY FIVE-YEAR PERIODS

Age	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44
Females....	18	27	15	26	68	89	88	68	44
Males.....	22	34	17	10	11	11	8	14	13
Total....	40	61	32	36	79	100	96	82	57
Age	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	Total
Females...	26	21	17	14	4	0	2	1	528
Males.....	15	15	14	16	8	1	1	2	212
Total....	41	36	31	30	12	1	3	3	740

nated, but they have been tabulated according to age at the time the case was recorded in 1912 or 1913. Chart 1 shows the age distribution of the total 740 cases, each individual being indicated by a plus sign in the column corresponding to the year of his age. Chart 2 shows the age distribution of the 528 female pellagrins and Chart 3 the 212 male cases. Certain inaccuracies are obvious in these figures, particularly the tendency for an excessive number of individuals to occur at the ages 25, 30, 35, etc., indicating that the exact age was sometimes not ascertained; and further the excess of individuals in the thirteenth year of age, which is undoubtedly an inaccuracy, probably resulting from evasion of the child-labor law, which has fixed the minimum age of mill-workers at 12 years.

Grouping together the cases in each five-year period, the distribution shown in Table 3 is obtained.

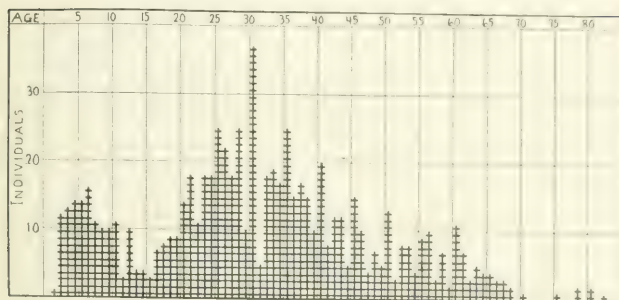


Chart 1.—Distribution of the 740 recorded cases of pellagra in Spartanburg County, according to age at time of record.

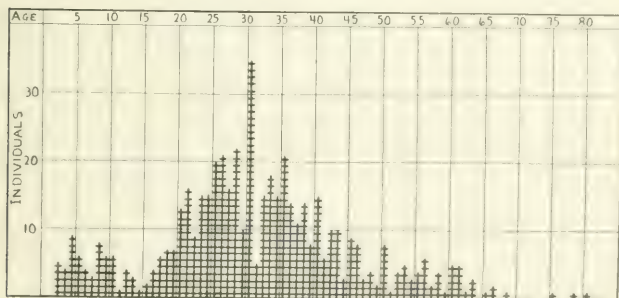


Chart 2.—Distribution of the 528 recorded female pellagrins in Spartanburg County, according to age at time of record.

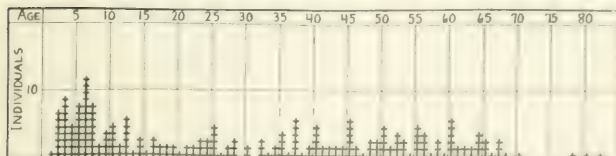


Chart 3.—Distribution of the 212 recorded male pellagrins in Spartanburg County, according to age at the time of record.

The data of Table 3 are shown in graphs in Chart 4.

By comparing the number of recorded pellagrins with the number of individuals in the county according to the United States Census of 1910, it has been possible to obtain an idea of the comparative pellagra morbidity in the age groups shown by the census returns. The data are shown in Table 4.

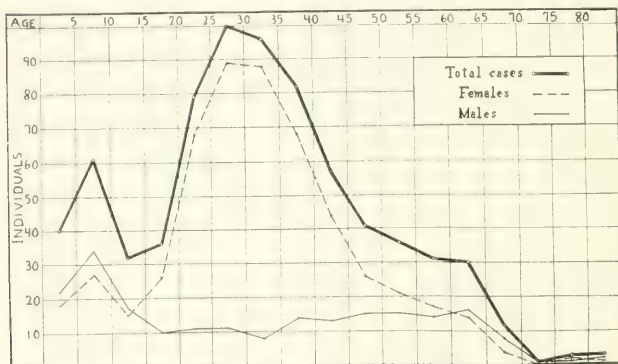


Chart 4.—Distribution of recorded pellagrins in Spartanburg County, according to age at time of record,\* grouped by five-year periods.

TABLE 4.—COMPARATIVE PELLAGRA MORBIDITY IN SPARTANBURG COUNTY IN THE VARIOUS AGE PERIODS

Age	Females			Males			Total		
	Popula- tion	Pella- grins	Morbid- ity per 10,000	Popula- tion	Pella- grins	Morbid- ity per 10,000	Popula- tion	Pella- grins	Morbid- ity per 10,000
0-4.....	7,431	18	24	7,763	22	28	15,194	40	26
5-9.....	4,364	27	62	4,490	34	76	8,854	61	69
10-19.....	10,954	41	37	10,906	27	25	21,860	68	31
20-44.....	13,417	357	267	12,822	57	44	26,239	414	158
Over 44....	5,509	85	154	5,652	72	127	11,161	157	141
Total....	41,675	528	127	41,633	212	51	83,308	740	89

The data of Table 4 are presented in graphic form in Chart 5. Unfortunately, it is possible to locate only five points on each of these curves, because census data for smaller groups of the population are not available.

The general relationships shown in these tables and figures are not significantly different from those shown in the First Progress Report,<sup>4</sup> although, of course, the number of cases of pellagra here considered is much larger and the indicated morbidity rate<sup>5</sup> correspondingly higher. In children the disease was about equally prevalent in the two sexes, the males showing a slight excess. In children under the age of 2

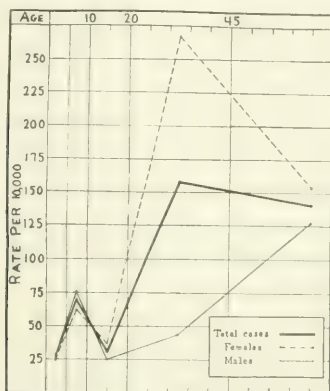


Chart 5.—Comparative pellagra morbidity per 10,000 population, according to age and sex, based on the 740 recorded cases in Spartanburg County up to 1913 and the population of the county as shown by U. S. Census, 1910.

TABLE 5.—NUMBER OF PELLAGRINS IN THE COUNTY IN EACH YEAR OF LIFE UP TO THE TWENTIETH

Year.....	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Female....	0	0	5	4	9	6	4	3	8	6	6	1	4	3	1	2	4	0	7	7
Male.....	0	1	7	9	5	8	12	8	2	4	5	2	6	1	3	1	3	2	2	2
Total.....	0	1	12	13	14	14	16	11	10	10	11	3	10	4	4	3	7	8	9	9

years we have record of only one case in Spartanburg County, a negro male, recorded as a pellagrin before he was 2 years old. In the third year there were twelve cases, thirteen in the fourth year and fourteen in the fifth year. The number of cases in each of the first twenty years of life for both sexes is shown in Table 5.

4. Siler, J. F., and Garrison, P. E.: *Am. Jour. Med. Sc.*, 1913, cxlvi, 54; First Progress Report, p. 28.

5. This is not the morbidity rate for a single year, but it is the ratio of total recorded cases to the population shown by the U. S. census in 1910. The bulk of the recorded cases of pellagra occurred in 1911, 1912 and 1913.

The figures are not very large, but they are large enough to indicate clearly that pellagra tended to attack children after their second year and that females from 11 to 17 years of age and males 13 years old and over were distinctly less frequently afflicted with the disease. After the seventeenth year pellagra morbidity has been increasingly higher in females, the number of cases rising rapidly until the age of 30, after which age the number of cases for each year gradually diminished, although the morbidity rate per 10,000 population remained high up to the period of old age (see Charts 2, 4 and 5). In males, on the other hand, there was observed no such sharp increase in pellagra, but only a slight and gradual rise in the number of cases, beginning at about

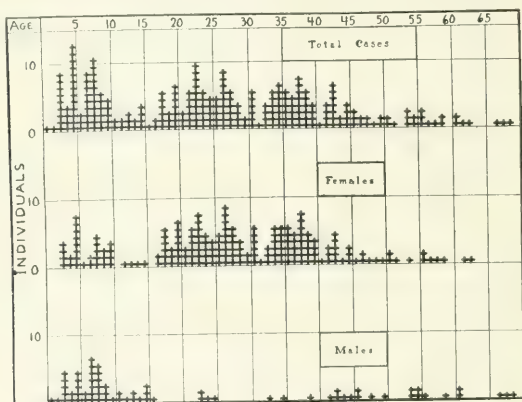


Chart 6.—Distribution of the 253 pellagrins (183 females and 70 males) present in 1913 in the seven villages, I., W., P., Sa., A., Sp. and B., according to age at onset of the disease.

the twenty-third year. The morbidity rate for males reached its maximum in old age, when it was approximately equal to the rate for females of similar age.

*Pellagra Morbidity in Seven Closely Studied Mill-Villages.*—The intensive house-to-house study of the population of the selected cotton-mill villages, which constituted the chief epidemiological feature of the work of 1913, has furnished an opportunity to study with peculiar accuracy the age and sex distribution of pellagra in a population in which the disease was excessively prevalent. For the present study we have available the approximately complete data in regard to age and sex of all pellagrins and of total population for six villages in Spartanburg County, designated as I., W., P., Sa., A. and Sp., and one mill-



village in Union County, S. C., designated as Village B. The total population of these seven villages was 6,599 and there were present in this population 253 pellagrins, of whom 183 were females and seventy were males. Figure 6 shows the age distribution by years of the total 253 cases, each individual pellagrin being assigned to his age at the time the disease first appeared, and in a similar way the age distribution of the 183 females and of the seventy males. Inaccuracies in the data, similar to those noted above in the data for Spartanburg County, are also evident here.

TABLE 6.—PELLAGRA MORBIDITY IN THE COMBINED POPULATION OF I., W., P., SA., A., SP. AND B. BY FIVE-YEAR AGE PERIODS TO AGE 20 AND SUBSEQUENTLY BY DECADES

Age	Females			Males			Total		
	Popula- tion	Pella- grins	Morbid- ity per 10,000	Popula- tion	Pella- grins	Morbid- ity per 10,000	Popula- tion	Pella- grins	Morbid- ity per 10,000
0-4.....	447	14	313	514	14	272	961	28	291
5-9.....	435	15	345	491	19	387	926	34	367
10-14.....	382	4	105	442	9	204	824	13	158
15-19.....	437	18	412	415	1	24	852	19	223
20-29.....	672	52	774	610	4	66	1,282	56	437
30-39.....	418	50	1,196	392	3	77	810	53	654
40-49.....	226	19	841	226	9	398	452	28	619
50-59.....	156	9	577	148	6	405	304	15	493
60-69.....	61	2	328	72	5	694	133	7	526
70-79.....	31	0	0	19	0	0	50	0	0
80-89.....	0	0	0	5	0	0	5	0	0
Total....	3,265	183	560	3,334	70	210	6,599	253	388

By grouping the pellagrins and the total population in five-year periods the distribution shown in Table 6 is obtained. In this table each pellagrin is placed according to his age at the incidence of his disease. The data for total population were obtained by our census in 1913.

The data of this table are presented in graphic form in Chart 7.

The same striking disparity between the morbidity rate of pellagra in females and the rate in males is presented by the figures derived from this intensive study of the mill-village population as has been found in our study of the age and sex distribution of the disease in the total population of the whole county in 1912 and again in 1913.

In children the disease first became important after the age of two, with nine cases in the third year, four in the fourth and thirteen in the fifth. The number of these cases in each year of the first twenty years of life is shown in Table 7.

At about the age of puberty and for a few years afterward, the number of cases was low in both sexes, rising rapidly again after the

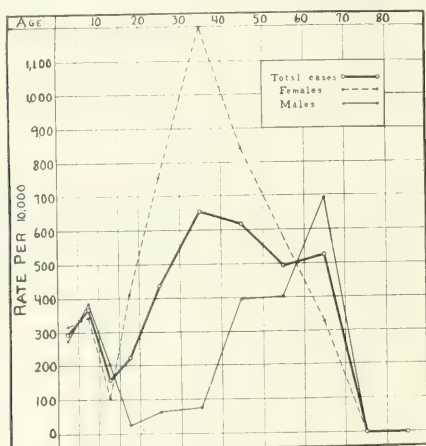


Chart 7.—Pellagra morbidity per 10,000 population of the seven villages, I., W., P., Sa., A., Sp. and B., according to age and sex, based on our census in 1913, data in Table 6.

TABLE 7.—NUMBER OF PELLAGRINS IN SEVEN MILL-VILLAGES IN EACH YEAR OF LIFE UP TO THE TWENTIETH, AGE AT FIRST ERYTHEMA

Year.....	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Female....	0	0	4	2	8	1	2	5	3	4	0	1	1	1	1	0	2	6	3	7
Male.....	1	1	5	2	5	2	7	6	3	1	2	1	2	1	3	1	0	0	0	0
Total.....	1	1	9	4	13	3	9	11	6	5	2	2	3	2	4	1	2	6	3	7

seventeenth year in the females to its highest point in the decade between 30 and 40 years of age, in which period 50 women, or about 12 per cent. of the women in this age period, were pellagrins. In the following decades the morbidity declined rapidly. There were 19 female pellagrins in the fifth decade and only 11 more than 50 years

old. In males, pellagra was somewhat more common than in females in the age period from 5 to 10. After the age of 15 the morbidity rate for males remained very low, comparatively, until the fifth decade, after which the two sexes appeared to be equally subject to the disease. Between the ages of 20 and 50 there were 121 female pellagrins and only 16 male pellagrins, while in the single decade from 30 to 40, there

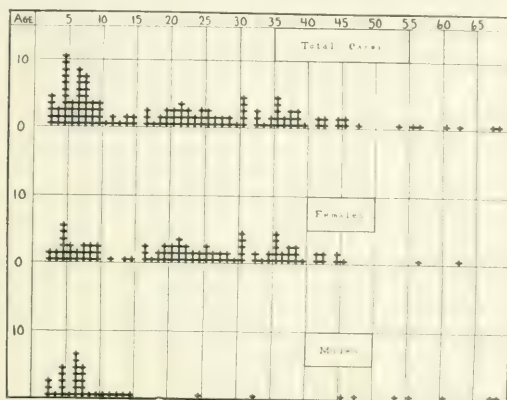


Chart 8.—Distribution of the 131 cases of pellagra (93 females and 38 males) which originated in the seven villages, I., W., P., Sa., A., Sp. and B., in 1912 and 1913, according to age at onset of the disease.

TABLE 8.—RATIO BETWEEN MORBIDITY RATE FOR FEMALES AND MALES IN EACH AGE PERIOD IN VILLAGES I., W., P., SA., A., SP. AND B.

Age....	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69
Females	1.0	0.8	0.4	18.0	13.0	16.7	2.1	1.5	0.4
Males...	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

were 50 female and only 3 male pellagrins. Reduced to its simplest terms, the ratio between the morbidity rate for females and for males in this population was as shown in Table 8.

The marked disparity between the morbidity of males and females during the active period of adult life is clearly evident.

*Incidence of New Cases in the Seven Mill-Villages.*—The figures just considered related to the total pellagrins present in these seven mill-villages and the total population present there at the time of our

census. It remains to consider the age and sex of the new cases of pellagra which are known to have developed in this population during 1912 and 1913. Some cases which arose in these villages in which the patients moved away before the time of our census in 1913 have been included in the data for this study, and in these instances the non-pellagrin numbers of such families have been added to the total population shown by the census, so that the total population employed in this study was approximately the total population of these villages, free from pellagra at the beginning of 1912. This amounted to 6,594 persons, of whom 3,260 were females and 3,334 males.

TABLE 9.—INCIDENCE OF NEW CASES OF PELLAGRA DURING 1912 AND 1913  
IN THE COMBINED POPULATION OF I., W., P., SA., A., SP. AND  
B., BY FIVE-YEAR AGE PERIODS TO AGE 20 AND SUBSEQUENTLY  
BY DECADES

Age	Females			Males			Total		
	Popula- tion	Pella- grins	Incidence per 10,000	Popula- tion	Pella- grins	Incidence per 10,000	Popula- tion	Pella- grins	Incidence per 10,000
0-4....	447	10	224	514	9	175	961	19	198
5-9....	435	14	322	491	15	305	926	29	313
10-14....	382	3	79	442	5	113	824	8	97
15-19....	432	9	208	415	0	0	847	9	106
20-29....	672	24	357	610	1	16	1,282	25	195
30-39....	418	24	574	392	1	26	810	25	309
40-49....	226	7	310	226	2	88	452	9	199
50-59....	156	1	64	148	2	135	304	3	99
60-69....	61	1	164	72	3	417	133	4	301
70-79....	31	0	0	19	0	0	50	0	0
80-89....	0	0	0	5	0	0	5	0	0
Total...	3,260	93	285	3,334	38	114	6,594	131	199

In this population there developed 131 recognized new cases of pellagra during 1912 and 1913, of which 93 were in females and 38 were in males. The age distribution of these cases is shown in Chart 8. By grouping together the incident cases of pellagra in each five-year period up to age 20, and subsequently by decades, and comparing these data with the total population in each group the incidence of pellagra for each age period has been ascertained. The figures are presented in Table 9.

The charts (Nos. 9 and 10) show the total population of each age period as a white column and within it a black column, indicating

## FEMALE POPULATION OF MILL VILLAGES I. W. P. SA., A. SP. &amp; B.

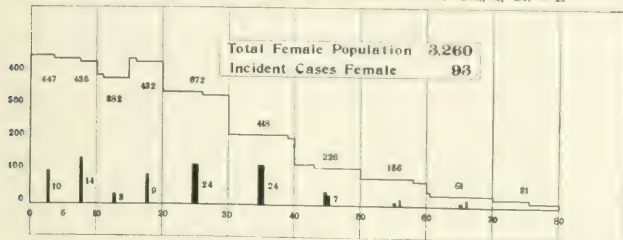


Chart 9.

## MALE POPULATION OF MILL VILLAGES I. W. P. SA., A. SP. &amp; B.

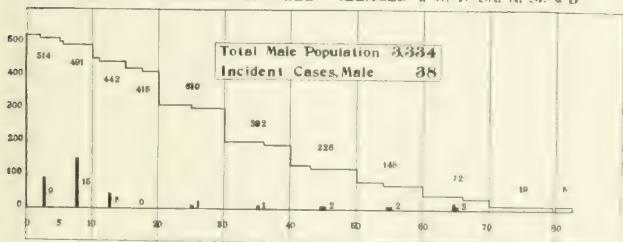


Chart 10.

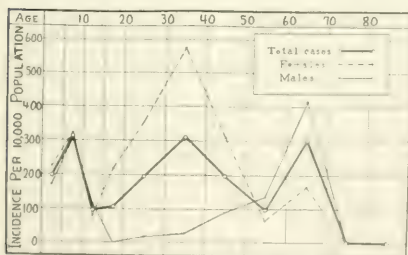


Chart 11.—Incidence of new cases of pellagra during 1912 and 1913, per 10,000 population, in the seven villages, I., W., P., Sa., A., Sp. and B., according to sex and age at onset of the disease, based on pellagra records of 1912 and 1913 and the census of 1913.

exactly by its relative area the proportion of the respective population which acquired pellagra in the two years, 1912 and 1913. These figures show at once the age distribution of the total population as well as of the incident pellagrins and their numerical relationship to each other. The incidence rate in each age group is shown graphically in Chart 11.

The incidence of pellagra in these villages was highest in females between 30 and 40 years of age, nearly 6 per cent. of this age group having contracted the disease during the two years. The next highest incidence was in old men from 60 to 70 years of age, of whom more than 4 per cent. (3 cases in 72 persons) contracted pellagra. The number of individuals in this group is so small that little significance can be ascribed to the incidence shown. In children from 5 to 9 years of age there were 28 incident cases in a population of 926 for this age period, an incidence of slightly more than 3 per cent.

TABLE 10.—RATIO BETWEEN INCIDENCE RATE FOR FEMALES AND MALES IN EACH AGE PERIOD

Age.....	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	Total
Females..	1.3	1.1	0.7	$\infty$ *	22.3	22.1	3.5	0.5	0.4	2.5
Males....	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

\* The rate for females in this group was 208 per 10,000; for males it was 0.  
 $\infty$  = infinity.

In order to compare more definitely the incidence of pellagra in females with that in males, the ratio for each age group has been reduced to its simplest terms by letting the rate for the males become unity in each instance (Table 10).

TABLE 11.—RATIO BETWEEN INCIDENCE RATES FOR DIFFERENT AGE PERIODS

Age.....	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	Total
Females..	0.8	1.1	0.3	0.7	1.3	2.0	1.1	0.2	0.6	1.0
Males....	1.5	2.7	1.0	0.0	0.1	0.2	0.8	1.2	3.7	1.0
Total....	1.0	1.6	0.5	0.5	1.0	1.6	1.0	0.5	1.5	1.0

In a similar manner the ratio of the incidence in each age period to the incidence in the total population of each sex has been reduced to its simplest terms, the incidence for the total females, total males and for the total population being unity in the respective ratios (Table 11).



These figures indicate the relative degree to which each age period was subject to the development of pellagra in the population of these seven mill-villages. Thus in females between 30 and 39 years of age the incidence rate was twice as great as for total females, while between 10 and 14 years the rate was less than one-third of this mean rate.

#### DISCUSSION

The peculiar distribution of pellagra in respect to age and sex, shown in these statistics, seems now to have been definitely ascertained for the population studied, more accurately, of course, for the seven villages than for the county as a whole. The inequalities of this distribution are pronounced and striking.

Children under 2 years of age were practically free from the disease, and yet from the age of 2 to 10 years children showed an excessive amount of pellagra. Congenital pellagra evidently did not occur in this study. Furthermore, the almost complete absence of pellagra in the first two years of life could hardly be explained as due to a supposed long incubation period of the disease, because there are many known instances in which the typical symptoms have developed in older persons within two months after moving into a pellagrous district, and furthermore, there have been some cases of typical pellagra in children less than a year old observed by various students of the disease. It would seem necessary, therefore, to conclude that children under 2 years of age in Spartanburg County have been physiologically insusceptible to the disease, or else relatively very little subjected or exposed to the causative agencies, or both. After the age of 2 this apparent protection from pellagra was no longer present, and the disease was very prevalent up to the age of 10 or 12 years, when the morbidity rate again declined. Apparently some change occurred at or near the age of puberty, which markedly reduced either susceptibility or exposure to pellagra and which persisted for some years. After the seventeenth year the females were again very subject to the disease, and continued to suffer at an increasing rate to the end of the fourth decade of life, while the males were practically free from the disease during this whole time. From 20 to 29 years of age, women in this population were 22.3 times more frequently afflicted with pellagra than men, and from ages 30 to 39 they were 22.1 times more subject to it. There was certainly some very important sex difference, either of susceptibility or of exposure to pellagra, or both, in these age periods. After 50 the sex difference in relation to pellagra was no longer evident and the old people of both sexes seemed to be about as frequently affected by pellagra as the children. The lower rate in females after 40 may have been due in part to the death of susceptible

individuals in the previous decade of life, but it would seem more probably due to physiological changes in the body associated with cessation of child-bearing and possibly to lessened exposure to pellagra-producing conditions. The rise in the pellagra rate for males at about the same time would seem to correspond with their diminished bread-winning activity and their increased tendency to remain at home.

It is necessary to recognize that the causes underlying this peculiar age and sex distribution have not been ascertained and that speculation in regard to its significance is likely to be erroneous. We are inclined to believe, however, that variation in physiological resistance has been a factor of considerable importance, and more particularly, variation in the vigor of the functions of digestion and nutrition. We also think that variation in degree of exposure to pellagra-producing causes, and more particularly to the supposed infectious agent, may account to some extent for these differences in age and sex distribution.

The high incidence rate of pellagra in children seems to deserve special emphasis because it has not been generally recognized. Many of these cases have been mild and would not ordinarily be brought to the attention of physicians. In the seven mill-villages there were 926 children from 5 to 9 years of age and twenty-nine of these developed pellagra during 1912 or 1913, an incidence rate for the two years of slightly more than 3 per cent. This fact is of particular interest not only because it indicates clearly the high incidence of pellagra in children in those communities where the disease is endemic, but also because of the relation of the incidence rate to the morbidity rate for these children. For the age group of children from 5 to 9 years of age the incidence rate was 313 per 10,000 and the morbidity rate 367 per 10,000, which means, of course, that about 85 per cent. of the cases observed in this age group had existed less than two years. In other words not more than 15 per cent., or about one in seven cases in children from 5 to 9 years of age, had a duration of more than two years. Inasmuch as deaths from pellagra have been rare in these children and the data of the above tables and charts show that few cases persisted into the next five-year age period, it is evident that a large proportion of pellagrin children in these villages must have recovered from the disease in less than three years from its onset. In the adult females between 30 and 39 years of age, on the other hand, the incidence rate in these villages was 574 per 10,000 and the morbidity rate 1,196 per 10,000, showing that there were many chronic cases, although deaths from pellagra in this age group were commonly observed. The general indication is clear that prognosis in pellagra is much better in children than in adult females. We hope to consider in a more definite manner the subject of prognosis in pellagra after our

cases have been followed for another year, but this indication of good prognosis in children is quite evident without any special study and seems worth calling attention to at this time.

*Synopsis.*—Pellagra was absent or very rare in children under 2 years of age, only very slightly prevalent for the five years following puberty in both sexes and only slightly prevalent in adult males under 50 years of age. On the other hand, it was enormously prevalent and severe in females from 20 to 40 years of age, somewhat less prevalent and nearly always mild in children of both sexes from 2 to 10 years of age, and almost equally prevalent in old people of both sexes. These features of the age and sex distribution are believed to be due in part to differences in physiological resistance to pellagra and in part to differences in frequency and extent of exposure to the disease, especially by proximity to or association with other pellagrins.

#### OCCUPATIONS OF PELLAGRINS AND THE POSSIBLE ETIOLOGIC RELATION OF OCCUPATION TO PELLAGRA

In the First Progress Report<sup>6</sup> was presented a table showing the occupation of 234 pellagrins on our records. In the present section those cases are again included. We have chosen now to present the cases in three separate groups: first, the pellagrins outside of mill villages; second, the pellagrins in mill-villages not studied by house-to-house canvass, and third, the pellagrins in the six mill-villages most intensively studied. The total number of pellagrins to be considered in these three groups is 726.

The group of pellagrins living outside of mill villages includes 313 individuals (223 females and 90 males). The female pellagrins living outside mill-villages had the following occupations: House work, 171; field work and house work, 35; no occupation, 11; teachers, 3; dressmakers, 2; clerk, 1; total, 223. The male pellagrins living outside mill-villages were distributed according to occupation as follows: Farmers, 37; no occupation, 14; laborers, 12; carpenters, 5; merchants, 5; salesmen, 3; machinists, 3; insurance agent, college student, clerk, butcher, railroad fireman, policeman, painter, blacksmith, printer, motorman and postmaster, 1 each; total 90. The 25 individuals (11 females and 14 males) having no occupation were children, a number of whom were attending school.

In the mill-villages other than those studied by a house-to-house canvass, there were 110 recorded pellagrins (74 females and 36 males). These cases were distributed according to age, sex and occupation as shown in Table 12.

6. Siler, J. F., and Garrison, P. E.: *Am. Jour. Med. Sc.*, 1913, cxlv, 62; First Progress Report, p. 37

The most striking features of these data appear to be the excessive prevalence of pellagra in the adult females engaged exclusively or for part of the time in house-work and the rather high incidence of pellagra in children under the age of 12 years. These observations are similar to those made in 1912 on the relation between occupation and the incidence of pellagra and, taken by themselves, would seem to support the conclusions based on our knowledge at that time, which were summarized in the First Progress Report<sup>7</sup> as follows:

The excessive prevalence of pellagra in the mill-village population is found largely among women and children at home during the day. Among actual mill-workers the rate of prevalence between the two sexes appears to be about equal.

Additional information on this question has been obtained during 1913. The complete census of several mill-villages has made it possible to compare the pellagrins with non-pellagrins in respect to occupation

TABLE 12.—PELLAGRINS IN MILL-VILLAGES NOT INVESTIGATED BY HOUSE-TO-HOUSE CANVASS, DISTRIBUTED ACCORDING TO AGE AND OCCUPATION

Age	Females						Males					
	No Occu- pation	House- Work Exclus- ively	House- Work and Mill- Work	Mill- Work, Full Time	Other Occupa- tion	Total	No Occu- pation	Farm- ers	Mill- Work, Part Time	Mill- Work, Full Time	Other Occupa- tion	Total
0-11	8	0	0	0	0	8	13	0	0	0	0	13
12-19	0	12	0	1	0	13	1	0	0	1	0	2
20-29	0	7	11	13	0	31	0	0	0	4	0	4
30-39	0	9	5	3	0	17	0	0	0	7	0	7
40-49	0	2	2	0	0	4	0	0	0	3	0	3
50-59	0	1	0	0	0	1	0	0	0	7	0	7
60-69	0	0	0	0	0	0	0	0	0	0	0	0
Total	8	31	18	17	0	74	14	0	0	22	0	36

and to compare the pellagra morbidity among females at home with the rate among females working in the mills. The data concerning age, sex and occupation of the 303 cases of pellagra (217 females and 86 males) which are known to have occurred in these six villages are summarized in Tables 13 and 14.

The morbidity of the mill-workers and of the remaining population is shown graphically in Chart 12.

7. Siler, J. F., and Garrison, P. E.: *Am. Jour. Med. Sc.*, 1913, cxlvi, 275; First Progress Report, p. 78.

A study of these tables brings out the fact that, so long as we consider only the proportion of house-workers and mill-workers among pellagrous women, the house-workers remain in a considerable majority. It was on data of this sort that our 1912 conclusions were based, inasmuch as exact statistics regarding the relative proportion of women working in the mills and about the house were not available for the non-pellagrin population. Our census study in the six mill-villages has disclosed the fact that the number of male mill operatives is considerably greater than the number of female operatives, instead of being about equal, as we supposed from our general inquiries in 1912, and in the light of this more accurate information the earlier conclusion that female mill-workers were less frequently affected by pellagra than house-workers has become untenable.

TABLE 13.—TOTAL RECORDED PELLAGRINS IN SIX MILL VILLAGES INVESTIGATED BY HOUSE-TO-HOUSE CANVASS, DISTRIBUTED ACCORDING TO AGE AND OCCUPATION

Females						Males					
No Occu- pation	House- Work Exclu- sively	House- Work and Mill- Work	Mill- Work, Full Time	Other Occupation	Total	No Occu- pation	Farm- ers	Mill- Work, Part Time	Mill- Work, Full Time	Other Occupation	Total
37	0	0	0	0	37	38	0	0	0	0	38
2	2	0	11	0	15	3	0	0	8	0	11
0	16	21	18	1	56	0	0	0	4	0	4
0	45	6	12	0	63	0	0	0	5	0	5
0	22	4	2	0	28	0	1	0	6	1	8
0	13	0	1	0	14	0	0	0	11	0	11
0	4	0	0	0	4	3	0	0	5	1	9
39	102	31	44	1	217	44	1	0	39	2	86

In the age period, 12 to 19, in which more than 80 per cent. of the individuals were employed in the mills, the pellagra morbidity was relatively low and the mill-workers were slightly less subject to the disease than those who did not work in the mills. The 94 females who did not work in the mills showed 4 cases of pellagra, a rate of 426 per 10,000, and of the 64 males 3 were pellagrins, a rate of 469 per 10,000, compared with rates of 229 and 150 per 10,000, respectively, in the mill-workers of like age and sex. In the persons over 20 years of age, in both sexes, the pellagra morbidity was generally somewhat higher in the mill-workers than in the total population. The female mill-workers between the ages of 20 and 50 show the highest morbidity.

*Synopsis.*—Persons engaged in many different occupations were found to be pellagrins, but the greatest number of cases was observed among persons engaged in house-work or remaining at home without

TABLE 14.—COMPARATIVE PELLAGRA MORBIDITY OF MILL OPERATIVES AND OF THE REMAINING POPULATION IN VILLAGES I., W., P., SA., A. AND SP., BASED ON TOTAL RECORDED CASES AND THE POPULATION STATISTICS OF CENSUS OF 1913

Age	Mill Workers			Other Persons			Total Population		
	Individ- uals	Pella- grins	Morbid- ity per 10,000*	Individ- uals	Pella- grins	Morbid- ity per 10,000*	Individ- uals	Pella- grins	Morbid- ity per 10,000*
FEMALES									
0-11.....	0	0	...	870	37	425	870	37	425
12-19.....	481	11	229	94	4	426	575	15	261
20-29.....	245	39	1,592	302	17	563	547	56	1,024
30-39.....	81	18	2,222	265	45	1,698	346	63	1,821
40-49.....	26	6	2,308	176	22	1,250	202	28	1,386
50-59.....	6	1	1,667	116	13	1,121	122	14	1,148
60-69.....	1	0	0	49	4	816	50	4	800
70-79.....	0	0	...	26	0	0	26	0	0
80-89.....	0	0	...	0	0	...	0	0	...
Total.....	840	75	893	1,898	142	748	2,738	217	790
MALES									
0-11.....	0	0	...	960	38	396	960	38	396
12-19.....	532	8	150	64	3	469	596	11	185
20-29.....	478	4	84	20	0	0	498	4	80
30-39.....	206	5	169	36	0	0	332	5	151
40-49.....	141	6	426	45	2	444	186	8	430
50-59.....	77	11	1,429	46	0	0	123	11	894
60-69.....	35	5	1,429	23	4	1,739	58	9	1,552
70-79.....	6	0	0	11	0	0	17	0	0
80-89.....	1	0	0	4	0	0	5	0	0
Total.....	1,566	39	250	1,209	47	390	2,775	86	310

\* The figures in the morbidity column of this table indicate the ratio of the number of recorded pellagrins to the number in the respective group of the present population. A considerable number of these pellagrins had died or moved away before the time of our census.

occupation, namely, the adult females and the children under 12 years of age. Occupation in house-work would appear, however, to bear only an accidental relation to this morbidity, because in those villages



concerning which accurate and complete data are available, the morbidity among female mill-workers was practically the same as among the housekeepers. It would appear that our studies have so far failed to discover reliable evidence that occupation has had any definite relation to pellagra morbidity. The excessively high pellagra morbidity in mill-villages would seem to depend on other circumstances affecting the various members of the village community, regardless of whether their days were spent at work in the mill or in other occupations or locations.

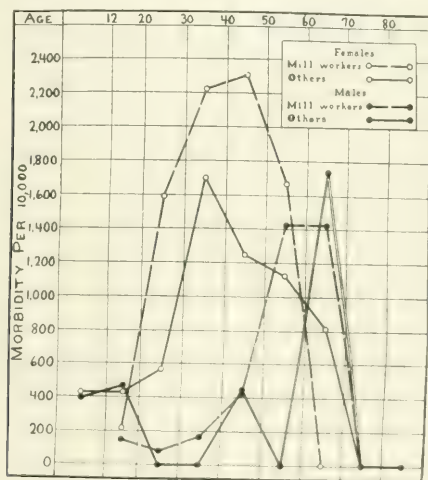


Chart 12.—Comparative pellagra morbidity in the six villages, I., W., P., Sa., A. and Sp., according to age, sex and occupation, based on the total cases of pellagra on record and the population statistics of the census of 1913.

#### SUMMARY

1. The geographical distribution of pellagra in Spartanburg County, South Carolina, has been uneven, the morbidity being much higher in and near the large centers of population and especially in the cotton-mill villages.

2. Pellagra was found to be about three times more prevalent in the white race than in the negro population of this county. This ratio is not regarded as a true measure of the relative racial resistance to the disease, but rather as the end result of the influence of several factors.

3. Women between 20 and 44 years of age have been most subject to pellagra. Children from 2 to 10 years of age, of both sexes, and

old people of both sexes have also been frequently attacked. Children under 2 years have been rarely affected; adolescents of both sexes and adult males under 50 years of age were relatively free from the disease. Pellagra in children has been relatively benign.

4. The peculiarities of the age and sex distribution are believed to be due in part to differences in physiological resistance to the disease and in part to differences in degree and frequency of exposure to the causative factors, among which proximity to or association with pellagrins seems to be important.

5. No direct relation of occupation to pellagra morbidity was discovered. Indirectly, by determining economic status and environment, occupation was found to have an important bearing on the prevalence of the disease.

## MENTAL AND NERVOUS DISORDERS ASSOCIATED WITH PELLAGRA \*

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The investigations here published were rendered possible by an invitation to undertake the study of this phase of pellagra extended to the author by the Thompson-McFadden Pellagra Commission. Permission to accept this invitation was readily granted by the Illinois State Board of Administration, to whom my respectful thanks are due. Most valuable assistance was rendered by the physicians of Spartanburg County, by Dr. J. W. Babcock, superintendent, and the medical staff of the South Carolina State Hospital, to one of whom, Dr. E. B. Saunders, I am especially indebted for information and assistance, and finally by the medical officers of the Georgia State Sanitarium. Dr. E. M. Green, clinical director, and Dr. J. W. Mobley, first assistant physician, especially gave of their time and wide experience with ungrudging courtesy. The whole medical staff vied with one another in assisting with the patients and records and contributed materially to such small measure of success as may have been achieved.

The extent of this subject is wide, and the time available was small. Many of the patients were seen but once and there was no possibility of continuous observation over a long period. With these facts in mind, it was thought best to try and observe the conditions at various stages by seeing as large a number of different patients as possible.

The material used comprises that obtained by visits to the homes of known pellagrins in and around Spartanburg, the examination of patients coming, or sent, to the offices of the Pellagra Commission for diagnosis and treatment, a closer study of cases cared for in the Good Samaritan Hospital at Spartanburg, and the investigation of patients and records at the South Carolina and Georgia State hospitals at Columbia and Milledgeville, respectively. To these have been added the results of experience with cases in Illinois.

So widespread is the belief in pellagrous districts, even among physicians, that pellagra is a potent factor in the etiology of insanity, and so greatly is the horror of this disease thereby enhanced in the

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minds of the people that the question is one of the greatest importance. Yet the actual state of our knowledge concerning the facts is extremely limited. Published statistics vary widely and most text-books, while very vague as to the details, seem to regard insanity as inevitable. Thus Wood says:<sup>1</sup> "It is true that the probable outcome of the ordinary types of pellagra will be insanity, and it is this phase which makes of the disease a great sociological problem."

#### FREQUENCY OF MENTAL SYMPTOMS

Most of the statistics concerning the frequency of mental disturbance in pellagra are of but small value for various reasons. First, they have been largely collected in hospitals for the insane, and it should be remembered that failure to commit a person to such a hospital is no criterion of the absence of mental disorder. It might also

TABLE 1.—INCIDENCE OF MENTAL SYMPTOMS IN RELATION TO THE NUMBER OF ATTACKS OF PELLAGRA FROM WHICH THE PATIENT HAS SUFFERED

	First Attack	Second Attack	Third Attack	Fourth Attack	Fifth Attack	Sixth Attack	Later Attack	Total No. of Cases
With mental symptoms .....	12*	17*	9	7	0	2	0	47
Committed as "In- sane" .....	2	2	1	0	0	0	0	5
Without mental symptoms .....	35	25	10	5	1	0	2	78

\* One of these committed suicide.

be said that many persons so strongly believe that pellagra is constantly associated with insanity that commitment may follow the placing of such a diagnosis without further consideration of the actual situation.

Secondly, it is not yet settled whether the recurrent outbreak of the symptoms of pellagra in succeeding years represents new disease each time or merely recrudescence following a period of latency. If the latter is true it would be obviously necessary to wait until the death of an individual before deciding whether he will ever become insane as the result of pellagra.

Thirdly, the statistics are based in the main on superficial estimates of the total incidence of pellagra in any given community, so that the case incidence of mental disorder becomes largely guess-work.

1. Wood, E. J.: A Treatise on Pellagra, D. Appleton & Company, New York, 1912, chap. vi, p. 224.

TABLE 2.—CASES SHOWING MENTAL SYMPTOMS IN DIFFERENT ATTACKS  
EXPRESSED IN PERCENTAGES

	No. of Cases	With Mental Symptoms, Per Cent.	Committed as "Insane," Per Cent.	Without Mental Symptoms, Per Cent.
First attack .....	49	24.5	4.1	71.4
Second attack .....	44	38.7	4.5	56.8
Third attack .....	20	45.0	5.0	50.0
Fourth attack .....	12	58.3	0.0	41.7
Later attacks .....	5	40.0	0.0	60.0
Total .....	130	36.2	3.8	60.0

TABLE 3.—AGE, SEX AND RACE RELATIONS TO THE INCIDENCE OF MENTAL  
SYMPTOMS

Age .....	1-10	11-20	21-30	31-40	41-50	51-60	61-70	Over 70
TOTAL CASES CONSIDERED								
	20	11	33	35	10	11	8	2

## PATIENTS WITH MENTAL SYMPTOMS

White males..	0	1	2	2	4	3	0	0
White females	0	1	10	13	3	2	2	0
Col. males....	0	0	1	1	0	0	0	0
Col. females...	0	1	4	1	0	0	1	0
Total .....	0	3	17	17	7	5	3	0
Proportion of total cases, per cent. ....	0.0	27.3	51.5	48.6	70.0	45.5	37.5	0.0

## PATIENTS WITHOUT MENTAL SYMPTOMS

White males..	9	2	0	1	0	6	2	2
White females	10	6	14	17	3	0	1	0
Col. males....	1	0	0	0	0	0	1	0
Col. females...	0	0	2	0	0	0	1	0
Total .....	20	8	16	18	3	6	5	2
Proportion of total cases, per cent. ....	100.0	72.7	48.5	51.4	30.0	54.5	62.5	100.0

TABLE 4.—AGE AND SEX RELATIONS EXPRESSED IN PERCENTAGES

	1-10	11-20	21-40	41-60	Over 61	Total
PERCENTAGE OF PATIENTS WITH MENTAL SYMPTOMS						
Males .....	0.0	33.3	85.7	53.8	0.0	36.8
Females .....	0.0	25.0	46.0	62.5	60.0	41.3
Total .....	0.0	27.3	50.0	57.1	30.0	40.0
PERCENTAGE OF PATIENTS WITHOUT MENTAL SYMPTOMS						
Males .....	100.0	66.6	14.3	46.2	100.0	63.2
Females .....	100.0	75.0	54.0	37.5	40.0	58.7
Total .....	100.0	72.7	50.0	42.9	70.0	60.0

The last source of error is a very important one. The experience of the Thompson-McFadden Pellagra Commission has demonstrated that, when an intensive study of a given pellagrous district is undertaken, far more cases are discovered than would be estimated from the most careful questioning of the physicians of that district.

In order to arrive at some data on this question the case records of 130 pellagrins, collected without any kind of selection except a positive diagnosis, have been analyzed and the results are presented in Tables 1 to 4. In preparing these tables no attempt has been made to subdivide the mental picture into different types, a point which will be considered later. It may be stated, however, that the great majority of cases included as "with mental symptoms," but not committed as "insane," were examples of a type which will be described as symptomatic depression. Such mental disturbances as well as milder forms of delirium occur in connection with many different diseases, especially the acute and chronic infections, and it may be objected that they do not constitute "insanity." In reply to this it is only necessary to point out that this latter term is not a medical one at all, and that no distinction can scientifically be made.

In this series of one hundred and thirty unselected cases, mental symptoms were present in fifty-two (40 per cent.), and of these, five (3.8 per cent.) were adjudged insane, while two others committed suicide. Certain other features also deserve mention. It will be noted that mental symptoms appear to be progressively more frequent the greater the number of the attacks. (This does not hold true in the above tables for cases having more than four attacks, but this may possibly be due to the small number of such examples.) In Tables 3 and 4, it is well shown that children with pellagra do not as a rule show



any mental disorder, and one may add from personal observation that they are generally not very ill with the disease. From the figures given it would appear that males between the ages of 20 and 40 suffer with mental symptoms far more than do females.

This is probably not without significance, although it must be admitted that the number of cases is very small (seven). When it is remembered that men of this age but rarely contract pellagra, it suggests that those who do are in all probability below the average in general make-up and hence especially liable to suffer from mental disorder.

The greatest case incidence of mental disorder in females, on the other hand, occurs between the ages of 41 and 60; that is to say, during the climacterium, a period during which, as is well known, women are especially prone to mental disturbance.

To supplement these figures, a similar analysis of a series of thirty-four consecutive cases studied by me and forming part of the material on which the later description of types is based, showed results entirely in keeping, except that the numbers are too small for subdivision into age groups. The percentage showing mental symptoms was 38.2. There were ten children of 10 years or under, none of whom showed any mental disturbance. The average age of those with mental symptoms was 41.5 years and of those without mental symptoms, 18.5 years.

As might be expected, there is also a correlation between the appearance of mental symptoms and the severity of the pellagra attack, as illustrated by the mortality given in Table 5.

TABLE 5.—CASE MORTALITY IN RELATION TO MENTAL SYMPTOMS

	No. of Cases	Deaths	Percentage Mortality
With mental symptoms.....	52	10	19.2
Without mental symptoms.....	78	2	2.6
Total .....	130	12	9.2

As a further illustration of this same point, it was found that in a series of eighteen patients, cared for and examined in the hospital provided for the Commission, who were admitted mainly because of the severity of the pellagra attack and the need for special attention, sixteen with an average age of 44 (23 to 95), showed mental symptoms, the exceptions being aged 10 and 15 years, respectively.

With the object of studying the question as to whether pellagra gives rise to a chronic "insanity" a list of all cases committed to the Columbia State Hospital from Spartanburg County from Jan. 1, 1912, to July 1, 1913, was secured, and these cases were investigated to determine how many were suffering from pellagra. These investigations were made possible by the courtesy of Dr. J. W. Babcock, super-

intendent, and the medical staff of the South Carolina State Hospital, the excellent records in the office of the Pellagra Commission and the physicians of Spartanburg County.

In 1912 sixty-five persons were adjudged insane in Spartanburg County, of whom eleven were stated to be pellagrous at the time of commitment. This diagnosis was confirmed at the State Hospital in all but one who had recovered from his attack at the time of admission. Besides these, nine others are reported as having pellagra at the time of admission to the hospital. In the first six months of 1913, twenty-four persons were adjudged insane, although only twenty-two were admitted to the State Hospital. Four were stated to be pellagrous on the commitment papers and to these must be added three found to have this disease when received at the hospital.

The population of Spartanburg County at this period was stated to be 83,465. The proportion of pellagrous persons living in the county, according to the figures of the Thompson-McFadden Commission in 1912, was 44, and in the first six months of 1913, 55 per 10,000.

These facts may be expressed in the accompanying table (Table 6).

TABLE 6.—CERTIFIABLE INSANITY IN PELLAGROUS AND NON-PELLAGROUS PERSONS IN SPARTANBURG COUNTY \*

	Total Number of Persons Committed	Number of Pellagrins Committed	Certified Insane per 10,000 Population	Certified Insane per 10,000 Pellagrins
1st. 6 mos., 1912...	28	9	3.3	245.2
2d. 6 mos., 1912...	35	14	4.2	381.5
1st. 6 mos., 1913...	24	7	2.9	152.2

\* It should be noted that the population has been considered as remaining constant throughout, and also that the number of living pellagrins in the first and second halves of 1912 has been regarded as equal. While not accurate, this will suffice for the present purpose. The figures for the whole of 1912 would be correctly given as the sum of those for the two halves of that year.

These figures as to the case incidence of insanity are somewhat smaller than those given by Grimm,<sup>2</sup> who found 7.5 per cent. insane of 1,436 cases. Presumably this refers to those who were certified as insane, and it is probable that the percentage is somewhat high for the reason that many of the milder cases of pellagra would not come under observation unless they were sought. Especially is this true, in the experience of the Thompson-McFadden Commission, for pellagrous

2. Pub. Health Rep., U. S. Pub. Health Service, March 7, 1913.

children in whom, as the figures already given amply demonstrate, mental symptoms are exceptional.

One other feature of the relation between insanity and pellagra, which has already been briefly mentioned, requires further consideration. That is the extraordinary frequency of pellagra arising in hospitals for the care of the insane. This fact of almost universal experience is well illustrated by the situation at Milledgeville, Ga. In Tables 7 and 8 are given, respectively, the numbers of cases of pellagra arising within and without the walls of the hospital in which there was an association with certifiable insanity.

TABLE 7.—PATIENTS ADMITTED WITH PELLAGRA ALREADY DEVELOPED\*

White							Colored						Total		
Male			Female				Male			Female					
	Admissions	Pellagrous	Per Cent.	Admissions	Pellagrous	Per Cent.	Admissions	Pellagrous	Per Cent.	Admissions	Pellagrous	Per Cent.	Admissions	Pellagrous	Per Cent.
910 ....	338	..	...	264	..	...	207	..	...	187	..	...	996	56	5.6
911 ....	365	14	3.8	281	31	11.1	212	5	2.4	206	20	9.7	1,064	70	6.5
912 ....	375	21	5.6	311	18	5.8	226	11	4.9	196	33	16.8	1,108	83	7.4
Total ...	1,078	35	3.2	856	49	5.7	645	16	2.5	589	53	9.0	3,168	209	6.6

TABLE 8.—CASES PROBABLY ARISING WITHIN THE HOSPITAL\*

	Average Daily Population	White		Colored		Total No. of Cases	Per- centage
		Male	Female	Male	Female		
1910 .....	3,276	..	..	..	..	114	3.5
1911 .....	3,383	12	16	10	61	99	2.9
1912 .....	3,424	35	27	21	97	180	5.3

\* These figures are taken from the annual reports of the Georgia State Sanitarium.

The population of the state of Georgia, according to the 1910 census was 2,609,121. If we accept the proportion of certifiable insanity for Spartanburg County as approximately correct for the state of Georgia, this would mean that in 1910 there were approximately 900 pellagrins (this figure is probably far too small, H. D. S.), or 3.4 per 10,000 of the population. On the other hand, the average daily

population of the hospital was 3,276 with 114 cases of pellagra, or 348 per 10,000, practically one hundred times as many as in the population outside. Experience in Illinois would tend to bear this out.

No satisfactory explanation of these facts has yet been offered. There are, however, several possibilities. First, if, as I fully believe, pellagra is an infectious disease, these hospitals may be endemic foci in which the opportunities for transmission are especially favorable. Secondly, it may be that the conditions of life are such as to cause pellagra, either by deficiencies in dietary, or positive intoxication by spoiled food or other means. Thirdly, and this is a possibility which has been too little considered, the conditions of life in such a hospital or the constitution of the persons therein confined may be such as especially to favor the onset of pellagra whether the actual cause be a living virus, a dietary deficiency or an intoxication. In discussing these possibilities it must be conceded that the only explanation for a special focus of infection in such a hospital would be the collection together of a large number of infected individuals sent to the hospital because of the occurrence of "insanity." This would not explain the sequence of events at the Peoria State Hospital and other institutions of like character in Illinois where the outbreaks appeared to start in these widely separated localities, while the number of cases in the state generally was certainly small. Some explanation is also needed for the rarity with which doctors or attendants in these institutions become affected. I know of no instance in Illinois. In Georgia but one was reported (J. E. II., white, male, attendant, on June 19, 1913) in the years 1910 to July, 1913.

The relation to dietary has already been discussed in the Report of the Illinois Pellagra Commission, 1913, so that there is no need to enter on that question here.

From the above consideration it therefore seems justifiable at present to state that evidence points to the conclusion that there is something in the make-up of those persons who suffer from faulty nervous organization, and especially of those who show character traits leading to what is called "insanity," which renders them more prone to affection with pellagra. This would be entirely in keeping with the statistics concerning the frequency of association between pellagra and insanity given above and elsewhere. It is too often forgotten that statistics merely establish correlations and do not indicate causal relationships. The importance of this view on the relation between pellagra and insanity will become more obvious from a consideration of the types of mental disorder which will be next considered.

## TYPES OF MENTAL PICTURE

The literature dealing with the forms of mental picture occurring in association with pellagra is not extensive and has been reviewed in an excellent article by Gregor<sup>4</sup> who also gives the results of his own investigations on this subject. He emphasizes the importance of distinguishing between the mental disorders which may be directly attributed to pellagra; i. e., are due to cerebral changes brought about by the pellagra toxin, and those which have only a secondary relation to it. As will be seen from the report which follows, my results agree in the main with those of Gregor, and there is but little need to discuss his findings separately.

The type of mental picture has also been studied in some detail at the Georgia State Sanitarium, where there is a large mass of material available for the purpose. At this hospital a system of classification has been adopted, under the advice of Dr. Adolf Meyer, which is free from objection, but which makes no attempt to particularize as to the relation between the pellagra attack and the psychosis. Such a method is unquestionably wise where the data are as yet scanty and the material undigested. Under this system all cases in which pellagra seems to have some relation to the onset of the psychosis are grouped together under the general title of "Psychoses Accompanying Pellagra." This group is then subdivided according to the condition-picture presented into subheads corresponding with the Kraepelin classification in general use. Thus there appear: Infective-exhaustive, manic-depressive, dementia praecox, involutional melancholia, general paralytic, paranoic and senile types.

At present, however, it seems justifiable to speak a little more definitely concerning the meaning of these types and their relation to pellagra. The situation, indeed, is much the same as that concerning the relation of many other general diseases to mental disturbance. As is well known, similar varieties of picture are met with in typhoid fever, yet they are not grouped separately because of this association. We recognize, it is true, that the toxins of this disease, like many others, directly injure brain, as well as other body cells; and that, in consequence of this damage, certain disorders in function, such as delirium, appear, which may be regarded as the direct result of the infection. On the other hand, there may appear a dementia praecox picture or a manic-depressive reaction and these cases run a similar course to that of other examples of these types in which there has been no such infection. It may be said that there are but few to-day who regard typhoid fever as more than a precipitating cause. Personally, I regard such

4. Jahrb. f. Psychiat. u. Neurol., 1907, xxviii, 215. Trans. by A. Alleman in *Alienist and Neurologist*, 1911, xxxii, No. 4.

reactions as this, whether following a specific fever or other somatic disease, or whether appearing in connection with some psychological difficulty, as the way of meeting difficulties of all kinds which are peculiar to this particular individual as the result of inheritance and experience.

Viewed in this light a dementia praecox type of picture and course is not a particular kind of disease, but merely the natural outcome of the particular kind of make-up with which the individual is endowed when placed face to face with difficulties which call for special adjustment. Thus, pellagra would not be the cause of the dementia praecox syndrome, but merely the last straw which brings the individual's modes of adjustment into prominence and demonstrates the odd and inadequate manner of doing things which have always been present, but which have not been specially obvious hitherto.

Indeed, there is another view of the relation between pellagra and insanity which deserves serious consideration and which has hitherto been but little discussed.

It is quite within the bounds of possibility that the actual relation between the functional psychoses (including dementia praecox) and pellagra is somewhat the reverse of that more usually accepted. That the defective construction, whatever it be, which is responsible for the poor adaptability and peculiarity of make-up indicated by the particular stamp of these disorders, predisposes to the development of pellagra. It is certainly a fact that the disease is extremely frequent among the chronic insane, most of whom represent late stages of the dementia praecox personality. This possibility should not be forgotten when considering the epidemiology of pellagra.

The relation of pellagra to psychoses due to more definite brain disease or degeneration, such as the presenile, senile and arteriosclerotic dementias, is a somewhat different question. That pellagra occurs in combination with them is unquestionably true, and it may be that such involutional changes and diseases as involve not only the brain but also the organs of the whole body, predispose to affection with pellagra. It is also conceivable that an intoxicative disease such as pellagra might favor the early onset of involutional change, or even actually provoke arterial degeneration in the course of time. But the relation of pellagra to the dementia thus arising would even then be secondary rather than direct.

The so-called general paralytic type has given rise to much discussion and deserves some special consideration, although I have so far been unable to see cases in which this description seemed justified. That pellagra occurs in individuals suffering from dementia paralytica is a fact of observation, as in a case recently seen with Dr. O. S.



Ormsby in Chicago. But this is not what is implied by this description. The cases here grouped have all been rapidly fatal and the picture presented is that of the final stage of dementia paralytica. It is not claimed that they run the whole course of that disease. To quote from the report by Green of Milledgeville, Ga., the features which lead to such a grouping are: "Exaggeration or loss of knee-jerk, speech disturbance [possibly a dysarthria due to stomatitis, H. D. S.], tremors, muscular incoördination, pupillary inequality or irregularity, convulsions and sensory disturbance." The case records of examples which I was able to study at the Milledgeville hospital speak of extreme disorientation with confusion and a muttering incoherence, so that but little information can be obtained from the patient who leads a more or less vegetative existence, does nothing for himself and voids urine and feces in the bed. The picture thus described suggests an extreme degree of general intoxication with central and possibly at times peripheral neuritis. It resembles in many respects the severe toxic forms of infective fevers, such as typhoid, and there seems but little justification for regarding it as especially comparable to dementia paralytica. It is not the extreme nervous disorganization which is characteristic of general paralysis, and it is unfortunate that a name with a specific significance should be used to describe a condition which may result from many different causes.

For purposes of description the types of mental disorder associated with pellagra may be grouped as follows:

Group I. Disorders directly due to the pellagra toxin (or toxins).

1. Symptomatic depressions.
2. Delirious pictures.

Group II. Disorders based on peculiarities in personal make-up, the "attack of insanity" being precipitated by pellagra.

1. Manic-depressive disorders.
2. Hysteria.
3. Psychasthenia.
4. Dementia praecox.
5. Paranoic developments.

Group III. Disorders due to definite brain changes with pellagra merely as a complication.

1. Arteriosclerotic dementia.
2. Senile dementia.
3. Presenile psychoses.
4. General paralysis of the insane.

The disorders in Group I may be considered in some detail, whereas the others will be passed over more briefly.

I. *Symptomatic Depressions.*—This type of disturbance is by far the most frequent, if one includes the cases outside a hospital for the insane. They are but seldom committed. They have been described by Gregor under the title of neurasthenic type, but the name here used seems preferable for the reason that while neurasthenic features are present, yet there is a decided attitude of depression, sometimes without any very definite objective signs of fatigue. The main characteristic of them is that the attitude of depression runs parallel with the other manifestations of pellagra, improving as they improve and becoming worse as these other symptoms become more severe.

The picture presented is that of a more or less hopeless sadness with all that this implies in regard to the activities of the body as a whole. There is a general lowering of tone, energy and attention are more or less difficult, thinking is difficult and activities are diminished. Obviously the exact mode of expression will vary with the personality of the patient, just as the words he uses to express his feelings depend on his personal experiences and habits of adjustment. As illustrations of the type most commonly met, the following quotations from cases observed in Spartanburg may be given: In expressing the color of the mood, "so blue I couldn't stand it hardly . . . seemed like I couldn't stand it if I couldn't sit down and cry"; "afraid I'll not get better"; "depressed and down-hearted"; "can't get cheerful"; "can't ever look forward to being any better." At times this is amplified by similes such as: "feel like I was lost . . . my soul was going to be lost and going to torment . . . didn't feel like I could get forgiveness for my sins." The lack of energy and feeling of inefficiency are shown in "energy and ambition all gone"; "can't do nothing, can't work or hold out"; "lost interest . . . it's hard to work"; "so tired all the time, no ambition"; "I just feel helpless"; "I used to be one of the best housekeepers and now look at my house." The difficulty in thought is shown in: "can't get my mind on anything"; "it's difficult to think"; "my recollection is mighty short"; "I'll get up from the porch to do something and forget what it is before I get into the house."

Sometimes there is more or less well-marked apprehension without any definite fear, e. g., "I feel as if something is going to turn up"; "so nervous I scream when anything happens." etc. At times this becomes definitely an anxiety expressed not only in words, but also by restless agitation. This has seemed to be true especially in persons during the involutional period of life and hence probably connected with the somatic changes which are then in progress, but it does also occur in younger individuals. Well-marked examples of this kind would naturally be included with the presenile psychoses or involu-

tional melancholia. In such case the pellagra is not the direct cause, but rather an exciting or perhaps purely complicating disease. Thus, for instance, I recently had under care in Illinois a woman in comfortable circumstances in life, who at the age of 58 developed an anxious agitated depression for which she was sent to a sanatorium. In the course of a few months she improved, although still depressed, and was returned to her home where she developed pellagra and became more worried and depressed, with finally the necessity of commitment at least three months after the onset of pellagra, but with active manifestations in the skin and gastro-intestinal tract. The condition ended fatally in a few weeks. Here unquestionably the sequence of events suggests that pellagra was merely a complicating disease and that the general bodily state expressed in the psychosis was a predisposing factor to, rather than the result of, its development. No other cases of pellagra had been known in the town in which this patient lived, although I am informed, one had occurred a year earlier in the sanatorium to which she was first sent.

*Delirious Pictures.*—By the term delirium is implied a state characterized clinically by clouding of consciousness together with sense-falsifications, especially of illusory character, the reactions of the patient in word and act being conditioned by this dream-like state. The vast majority of such condition-pictures are the result of intoxication of the brain with consequent general lowering of functional activity which involves first and most the highest cerebral levels. All degrees are met with in pellagra as in other intoxications. In the milder forms the periods of clouding may be quite brief and episodic. In such cases, in the intervals when consciousness is practically clear, the general attitude is one of symptomatic depression similar to those described above. Indeed, it is not uncommon to find that the more severe forms of depression give a history of occasional and transient sense-falsification with apprehensive content and more or less fear-reaction. Such, for instance, is true for Case 1, recorded below, while Case 2 represents a more severe and permanent clouding with practically complete amnesia for the period on recovery.

*CASE 1.—Symptomatic depression with episodic clouding, sense-falsification and apprehension. Central neuritic syndrome and fatal outcome.*

B. S., white woman, aged 35, observed first at home and later in the Good Samaritan hospital. The family history as far as obtained was negative for mental and nervous disease. The patient was stated to have been healthy except for malaria in childhood. The first attack of pellagra appeared in April, 1910, and subsided in the following month, but was accompanied by some depression. The second attack was very similar and appeared in April, 1911.

The third attack of pellagra was more severe and began in April, 1912. This was accompanied by severe gastro-intestinal symptoms and was still present in July when she was examined by the commission, who state that she then was very weak, much depressed and did not seem at all times to be quite clear in

her mind. This outbreak gradually subsided, but the erythema recurred again in December, 1912, with an exacerbation in January or February, 1913.

Mental picture: July 16, 1913. The patient appeared very dull and apathetic, intensely depressed, "life is not worth living," spoke in a low, rather monotonous voice, slowly and only with frequent urging. She seemed to be entirely clear and perfectly oriented as to her surroundings and the situation. When left to herself she lay in bed almost without movement, paying but little attention to what was taking place around her.

In answer to questions she expressed a feeling of fear, at times severe, as if "something going to get me." She mentioned the occurrence of "bad dreams" in which she would see horrible things, animal forms which she could not describe. She would also hear voices, even when awake, some of which were recognized, others were strange. They frightened her but she could not give the content more than to say that they were "just calling me." There was at the time of examination a full realization that they were imaginary but "they just come by spells" and at such times seemed real. In answer to a leading question she stated that at such times she did not feel clear in her mind.

Such periods as this came irregularly and lasted perhaps a day but she could not give any details as to frequency. The picture of hopeless apathy continued during the week that she was under observation, without the appearance of any objective evidences of clouding or apprehension. There was, however, a rapid development of signs of a "central neuritis" reaction, gross exaggeration of deep reflexes, bilateral extensor plantar reflex, slight jactatoid movements, nausea and vomiting. In spite of a temporary improvement in the last few days of July, the patient died August 9, 1913.

*CASE 2.—Delirious type. Severe clouding of consciousness with sense-falsifications of dream-like character and of depressive and more or less horrible content. After about four weeks a brief period of apathetic stupor and recovery with amnesia; subsequent exacerbation with fatal outcome.*

S. M. P., white woman, aged 23, housewife. Admitted July 11, 1913. The friends and relatives were very ignorant and the history is consequently not full. As far as could be determined, the family history showed nothing of importance for two generations. The patient was always healthy and had no serious illness. She had some attacks of "fever," but was at no time out of her head. The family were in poor circumstances and she had no schooling. She was described as of quiet, retiring disposition, high-tempered and "some selfish." She was, however, contented and cheerful, "would sing right smart" and worked steadily. Always scrupulously neat and clean, "an excellent house-keeper," "nothing ever out of order." She was married about two years ago; has been happy and has one child about 1 year old.

Pellagra: The first attack occurred in the summer of 1912, five months before the birth of her child. She then had a characteristic erythema of the hands with stomatitis and diarrhea. She was not very ill and is said to have had no mental disorder except "some loss of memory" and a general malaise. These symptoms all cleared up during the summer, although there is said to have been some scaling of the hands more or less until the present attack. Towards the end of May, 1913, the hands again became sore and soon after there appeared sore mouth and diarrhea.

Mental disturbance: About the beginning of the last week of June, 1913, the patient became "queer in her head." She seemed "to be hearing voices and talking to them." At first more or less intermittent this condition has become worse and practically continuous with increasing restlessness and fearful excitement. Many of her utterances were quite unintelligible even to her relatives, but the general trend is illustrated by such remarks as she had "seen her mother dead," her "head cut off," etc. At times she would suddenly "jump up like she was going to run away," and the restlessness had become so extreme as to make it difficult to care for her. During this period she had been growing steadily weaker and had emaciated badly.

When admitted to the hospital she was extremely ill, with severe and characteristic erythema, stomatitis and diarrhea. When seen by me, July 14, 1913, no very complete examination was possible owing to the extreme illness of the patient, but no evidence of other somatic disease was discovered. Neurologically there was marked exaggeration of the deep reflexes but without clonus, and the plantar reflexes were of flexor type. Constant restless movements were present, tossing about in bed, pulling at the bed clothes and even trying to get out of bed. All these movements were feeble and tremulous but showed no incoordination and there were no convulsive jerkings or twitchings.

All the time the patient was muttering, with occasional crying or apprehensive screaming. Much of what she said could not be understood, partly because of the low muttering, and partly because of the dysarthria due to severe ulcerative stomatitis. Samples of spontaneous utterances are: "Give it here . . . give it here . . . Oh! get up . . . get loose from there . . . I can't do nothing . . . (pulling at the bedclothes and looking around apprehensively) . . . I wouldn't use you that way . . . Oh! . . . Oh! . . . you're on my dress . . . I want my dress . . . (cries and moans fretfully and becomes unintelligible)." "I go up and go all over the place . . . go from here to the mill . . . and never know what is the matter . . ." "Annie . . . Annie . . . Annie . . . Oh! . . . Oh! dear (screams) . . ."

During this time she was apparently taking no notice of her surroundings, paid no attention to the examiner or her sister when they entered the room nor to the fact that someone was sitting close beside her. By speaking loudly and persistently it was possible to gain some degree of attention and even some degree of relevancy in response. When asked her name she did not give it but when asked to spell it said somewhat slowly and monotonously, "R - i - n - e - e - n - h - e - a - e - a - h - e - a - t - a - t - a - t" (her maiden name was Rhinehart). She gave the name of her home town correctly, but when asked her father's name gave that of her husband. When asked if she was sick she replied, "Of course I am . . . Go away from here . . . I don't want to talk to you . . . I want to go home . . . Annie . . . Annie . . . Oh! . . . Oh! . . . dear." Questioned as to her baby she said that "she (the baby) is dead." This is not true but is an illustration of the depressive content of the ideas. No answer indicating any grasp of where she was could be obtained and she apparently failed altogether to recognize her sister or brother-in-law.

She virtually did not sleep the following night, but screamed and yelled as if in fear or in pain. The next morning, however, she was a little brighter when roused, recognized her sister and called her by name, but immediately again became more clouded and presented a picture much as before.

July 17 she was obviously clearer and more easily roused but fretted and moaned much of the time. She then stated that she "felt terribly bad" and spoke spontaneously of a visit from her sister and mother (the latter had not been there) and added that she had not seen her husband. With regard to herself she said "seems like I have just given way and haven't got any use to myself . . . I can't get up . . . couldn't do nothing." When questioned about her baby she replied that she was "doing nicely, thank you." She very speedily became tired and more fretful and denied any knowledge as to her whereabouts.

From that time she became gradually brighter when roused but at the same time more heavy and apathetic when left to herself. It was not until July 22 that she was able to recall the name of the hospital or the examiner, although these had been told to her repeatedly. At this time she said she was "feeling good" but very tired. She stated "I've got my mind now . . . have for a long time . . . I used to didn't have none, didn't know nothing." In answer to question she professed to be entirely ignorant as to what had happened for two or three weeks but came to herself "last week." She spoke of the period

as being "all like a dream," but was apparently unable to remember any of the dream.

Coincident with the improvement in the mental state the pellagrous symptoms had been improving. The skin eruption was almost gone on July 20 and the diarrhea, after becoming gradually less, ceased altogether about July 22. She remained weak but clear mentally until September 1, when she became stuporous and died September 7.

Occasionally, periods of delirium recur several times in relation with exacerbations in the general manifestations of pellagra. One such example was seen at Milledgeville in the case of T. S., a colored man, who had four such brief periods of apprehensive excitement in which he vaguely remembered horrible "dreams" of being pursued by wild animals and tortured by persons in his environment with whom he fought. These "dreams" explain his conduct as observed during the attacks and each occurred in association with an exacerbation of diarrhea.

The relation of pellagra as the cause of such attacks is fully intelligible, but it should be remembered that different individuals show different relations to intoxication. Some very easily become delirious from alcohol or mild infectious fever; others seem able to resist much larger doses and more severe infections. It is thus generally recognized that the persons who readily develop delirium are poorly constructed in some way. The fact that delirium occurs so frequently in pellagra is capable of two explanations. Either the toxin is extremely virulent, or the individuals who suffer from pellagra are especially those of poor nervous organization. This latter possibility is in keeping with the suggestions already made in this direction.

II. *Disorders in which the Character of the Picture is due to the Personality of the Individual Affected.*—It would be entirely out of place here to attempt to describe these pictures. They differ in no way from other examples of such types not associated with pellagra. It is true that the pellagrous intoxication may give rise to a delirious stamp which may render the recognition of the type more difficult, but such features, as in the deliriums already described, will run a course parallel to the other pellagrous manifestations, whereas the elements in the disorder belonging to the personality of the patient will remain more or less independent of them.<sup>5</sup> This is also the case with examples of such psychoses arising in connection with specific fevers. Dementia praecox precipitated by a puerperal infection may be recognizable at first only as a delirium, which disappears with the subsidence of the infection, while the peculiar traits of conduct which make up the dementia praecox picture become thereby more and more obvious.

It may be said, then, that disorders of this kind run a similar course with a similar outcome (except that the pellagra brings with it a far

5. See Case 2 "Pellagra in Illinois," THE ARCHIVES INT. MED., 1912, x, 162.



greater menace to life) to that of cases arising with some other factor as a precipitating agent. The dementia praecox types result in what is called deterioration or dementia, the manic-depressive modes of reaction subside after a shorter or longer time without dementia, and so on.

In cases of this kind which have been investigated by me, evidences of the type of personality which results in such developments have been demonstrable before the onset of pellagra. An excellent illustration is afforded by a typical outbreak of manic excitement coincident with the appearance of pellagra which led to the first commitment of the patient.<sup>6</sup> The anamnesis revealed evidence of a manic-depressive type of make-up for several years before.

An excellent example of a dementia praecox picture, with apparent recovery, was seen at Milledgeville. A very full katamnesis was obtained in which it was learned that the fancies and imaginations with peculiar forced reactions had been present, although unknown to relatives, for at least nine months before the outbreak of pellagra, which did not become quite definite until after admission, although suspected at the time when she was received. Another patient was seen at Columbia with considerable deterioration, of the dementia praecox type, who had been admitted to the hospital on several occasions with attacks of pellagra, but in whom the mental disorder, as stated by Dr. Saunders, had been present at least one year and a half before the first attack of pellagra.

Below is published in detail another case (Case 3), probably belonging to the dementia praecox group, but with certain other features of nervous disease which seemed worthy of record. The absence of any parallelism between the pellagra and other nervous manifestations is here obvious.

These illustrations might be multiplied without advantage, sufficient having been said to illustrate the point under consideration. It may be that cases occur in which the sequence here claimed cannot be demonstrated, but where it has been possible to obtain sufficient information, no case has yet been presented to controvert this claim. Both at Milledgeville and Columbia an effort was made to see every pellagrous patient who had been detained as an example of chronic insanity.

With regard to Group III, there will be but little objection to the views expressed, that the pellagra and nervous disease are separate disorders, although it is possible that some degree of correlation may exist, in that one may predispose to the other. The question of a general paralytic type has already been discussed and need not detain us here.

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6. See Case 3, "Pellagra in Illinois," *THE ARCHIVES INT. MED.*, 1912, x, 166.

## FREQUENCY OF THE DIFFERENT TYPES OF MENTAL PICTURE

This subject may be considered under two headings. First, the frequency in a series of cases of pellagra, and second, the frequency in a series of cases committed to a hospital as "insane." The material at hand is not entirely satisfactory for this purpose owing to the short time available. For the first part of the question, use will be made of the cases in which the patients were seen and examined by me, and of the 130 observed by the Pellagra Commission. The information in these latter cases is not always sufficient to justify a positive conclusion, but the errors will be small.

TABLE 9.—TYPES OF MENTAL DISORDER IN A SERIES OF PELLAGRINS

	Thirty-four Unselected Cases Seen by the Author		One Hundred and Thirty Unselected Cases Seen by Commission		Total Unselected Cases		Eighteen Hospital Cases Selected for Severity	
	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.
Group I—								
Symptomatic depression	9	26.5	41	31.5	50	30.5	10	55.5
Delirious pictures.....	2	5.9	10	7.7	12	7.3	2	11.1
Group II—								
Manic-depressive disorders	0	0.0	0	0.0	0	0.0	1	5.5
Hysterical disorders.....	1	3.0	0	0.0	1	0.6	0	0.0
Dementia praecox dis- orders .....	0	0.0	1	0.8	1	0.6	1(?)	5.5
Group III—								
Arteriosclerotic dementia	0	0.0	0	0.0	0	0.0	1	5.5
Presenile psychoses.....	1	3.0	0	0.0	1	0.6	0	0.0
Senile dementia.....	0	0.0	0	0.0	0	0.0	1	5.5
Total .....	13	38.2	52	40.0	65	39.6	16	88.8

For the second part, use has been made of the thirty pellagrins committed to the Columbia State Hospital from Spartanburg County. To these are added the figures obtained from the annual reports of the Georgia State Sanitarium. Many of the records of these cases and some of the patients were investigated by me, so that some discussion is permissible.

From Table 9 it will be seen that in a series of 164 unselected cases of pellagra, mental symptoms directly attributable to this disease occurred in 62 or 37.8 per cent.; that 2 (1.1 per cent.) presented a psychosis depending on peculiarities in personal make-up, and that 1 (0.6 per cent.) showed the mental picture of an involutional psychosis.

From the above Table it will also be noted that in the 164 unselected cases of pellagra the disorders included in Group I constitute 95 per cent. (62 out of 65 cases) of the mental pictures observed in the series.

One is probably not justified in attempting to correct the groupings here given of the Georgia cases, because in many instances the patients were no longer in the hospital and the time available for a study of those remaining was very short. Nevertheless, it may be pointed out that the cases included under the head of "general paralytic type" seemed to be severe examples of delirium (none of these patients were seen) and that some of the manic-depressive depressions appeared to belong rather to our group of symptomatic depression. Of all the fifteen cases of dementia praecox type only four were still present in

TABLE 10.—TYPES OF MENTAL DISORDER ASSOCIATED WITH PELLAGRA ADMITTED TO THE GEORGIA STATE HOSPITAL IN 1911 AND 1912, TAKEN FROM THE ANNUAL REPORTS OF THAT INSTITUTION, AND OF THOSE ADMITTED TO THE SOUTH CAROLINA STATE HOSPITAL FROM SPARTANBURG COUNTY IN 1912 AND THE FIRST HALF OF 1913

	Georgia Cases				Columbia Cases				Per Cent. of Grand Total
	1911	1912	Total	Per Cent. of Total	1912	1913	Total	Per Cent. of Total	
Group I—									
Symptomatic depression...	0	0	0	0.0	2	1	3	10.3	1.7
Delirious pictures*.....	38	46	84	54.9	16	4	20	68.9	57.1
General paralytic type†...	6	2	8	5.2	0	0	0	0.0	4.4
Group II—									
Manic-depressive disorders	8	10	18	11.7	2	0	2	6.9	11.0
Dementia praecox disorders	9	6	15	9.8	2	1	3	10.3	9.9
Paranoic disorders.....	0	1	1	0.7	0	0	0	0.0	0.6
Group III—									
Involuntional psychoses...	2	1	3	1.9	0	0	0	0.0	1.7
Senile dementia.....	2	0	2	1.3	1	0	1	3.4	1.7
Undetermined types.....	5	17	22	14.4	0	0	0	0.0	12.1
Total .....	70	83	153	100.0	23	6	29	100.0	100.0

\* In the hospital reports these cases are grouped under the title of infective-exhaustive types.

† These in all probability belong with the delirious pictures.

July, 1913. In them the grouping seemed justifiable. Of the others, some were dead and the records at times suggested rather a delirious picture, while others had been discharged. A study of the records of the cases in which no type had been determined naturally permitted no conclusions, but it may be said that death followed speedily in many of the cases and this suggests that many of these patients belong in the delirious type.

Leaving the figures as given in the hospital reports it is obvious that delirium is by far the most frequent form of mental picture which leads to commitment. The effect of reclassification would be only to

augment this group at the expense of the others. It would be a matter of great value and interest if the subsequent history as regards outcome of the psychosis could be followed in detail for all cases in these various groups.

If one compares the proportion of the different groups in Table 10 with that in Table 9, it will be obvious that a very erroneous impression of the relative frequency of the different types of mental disorder associated with pellagra would be gained if the data were limited to the cases admitted to a hospital for the insane. Group I constitutes 95 per cent. of all forms in Table 9 and but 63 per cent. (as a minimum) in Table 10.

One other comparison may be made at this point which tends to emphasize the correlation between faulty nervous organization and liability to pellagra. According to the annual report of the Georgia State Sanitarium for 1912, there were admitted to that hospital 132 cases of dementia praecox and 150 cases of manic-depressive insanity. Among the pellagrins it will be seen from Table 10 that there were six examples of a dementia praecox type of personality, and ten of manic-depressive constitution. The ratio between pellagrous and non-pellagrous individuals in the two groups is 1:22 and 1:15, respectively, proportions which are unquestionably far greater than that of pellagrous to non-pellagrous sane inhabitants of the state of Georgia.

#### OUTCOME

From a practical point of view, this is probably the most important question of all. The facts recorded above afford ample justification for the general recognition of the frequent association between insanity and pellagra. But they do not support the gloomy prognostications which are so prevalent and so distressing in pellagrous regions.

It will be noted that of all the examples of mental disorder occurring in a series of 164 unselected cases, 95 per cent. are included under the heading of symptomatic depression or delirium. Furthermore, that of the cases committed as "insane" at least 63 per cent. come under this same category. All of these cases will recover provided they live through the attack of pellagra. The mental symptoms bear exactly the same relation to pellagra that the similar disturbances occurring in connection with other infective or intoxicative diseases, such as typhoid and tuberculosis, do to these diseases. They do not lead to any permanent mental disorganization.

This at once brings up the question as to whether there is any form of chronic insanity which can be considered as being directly due to pellagra. This question is necessarily closely bound up with the view which is taken as to the rôle which is played by pellagra in the etiology of dementia praecox. This has already been discussed and the view

expressed that such a development is the result of the personality of the individual rather than the consequence of the disease process which constitutes pellagra. Many of the examples of these types have shown definite mental disturbance prior to the outbreak of pellagra. It would be impossible to say definitely that all others would have developed the psychosis if they had not contracted pellagra, but there is no doubt in my mind that the probabilities are strongly in favor of such an occurrence. For, difficulties to be faced must occur in even the most protected existence and it becomes a question of the degree of ability possessed by the individual to adjust in a manner which more or less satisfactorily meets the difficulties. The answer to this question is the determining factor in the evolution of a psychosis. In other words, such a personality must be considered as always standing on the edge of a precipice over which he may slide as the result of any difficulty whatsoever, provided it cause him sufficiently to stumble. The man with average capacity for walking amid the irregularities of the pathway of life will successfully maintain his poise, while he with poorly balanced mechanisms of coordination or adaptation is liable to fall.

Besides this form of dementia, it is also possible that, like alcohol, pellagra might produce a degenerative condition in the nervous system with resulting chronic dementia. While this possibility cannot be denied, I can state definitely that in spite of a close search for examples of such end-result I have as yet failed to find one. At Milledgeville, an attempt was made to interview all still present patients with "psychoses accompanying pellagra," with this question in view, but without result. It may be that I am including some examples of this kind with the terminal stages of dementia praecox, but the number is certainly small and in my opinion entirely negligible.

It thus seems justifiable to conclude that pellagra is especially frequent in individuals of faulty nervous organization, and that in consequence there occur, in association with it, a greater percentage of such disorders as dementia praecox, manic-depressive insanity, hysteria, etc., than prevails among more healthy persons, yet the vast majority of the mental disturbances occurring in connection with pellagra are of no more significance *quâ* "insanity" than are the deliriums of typhoid fever. It is, however, probably true that, just as in that disease, the appearance of delirium or severe depression is a sign of the severity of intoxication and greater danger to life.

#### NERVOUS MANIFESTATIONS

This subject will be dealt with extremely briefly, for the reason that there is but little to add to what has already been said by me in the report of the Illinois Pellagra Commission. One cannot but be

impressed with the strong conviction which prevails that pellagra is especially a disease of the nervous system. Thus we find Wood<sup>7</sup> stating, "It is a daily problem with me and my colleagues to differentiate between myelitis of specific origin and similar pathologic conditions produced by pellagra."

Among the cases seen in the South, apart from the results of arteriosclerotic changes such as cerebral thromboses, it has been my experience to observe only one case in which there were evidences of chronic structural change in the nervous system. (This is entirely in keeping with the findings in regard to chronic dementia.) It is true that many of the severe and fatal cases present the syndrome of central neuritis, which is a reaction of the central nervous system to severe intoxication. This subject has already been amply discussed in the Illinois report and the anatomical findings in a series of cases published by L. J. Pollock and myself.<sup>8</sup> Dr. E. B. Saunders kindly furnished me with information as to the mode of death among pellagrins in the Columbia State Hospital. According to her observations, in a series of 88 fatal cases, sixty-four patients (74.7 per cent.) died with central neuritic symptoms, nineteen (21.6 per cent.) with appearances of simple exhaustion and five (5.6 per cent.) terminated suddenly from some unknown cause. In all severe cases there are evidences of irritable weakness in the nervous system, such as tremors, exaggeration of tendon-jerks, increased myotatic irritability, etc., entirely comparable to those met with in other severe intoxicative conditions, such as tuberculosis. Occasionally loss of knee-jerk is reported, the exact meaning of which is not always clear. The only example in the series here reported in which such a loss existed was that of an old man with severe arteriosclerosis who had suffered from a cerebral insult before the onset of the pellagra. The right knee-jerk (on the side of the hemiplegia) was present, but faint, while the left was absent. In the light of other experience, it seemed more probable that the lost knee-jerk was associated with some cerebral lesion rather than with the pellagra.

The single instance of chronic nervous disease which has come under my observation is deemed worthy of record in detail.

CASE 3.—"Shut-in" type of personality. Loss of interest following first attack of pellagra. More definite psychosis of dementia praecox type of about nine months' duration ending in apparent recovery after a second attack of pellagra. Occasional sudden brief attacks of loss of power in the lower extremities since the first attack of pellagra. Atrophy of small muscles of hands and spastic paraplegia of gradual evolution following the second attack of pellagra.

7. Wood, E. J.: Treatise on Pellagra, D. Appleton & Company, 1912, p. 228.

8. Singer, H. D., and Pollock, L. J.: The Histopathology of the Nervous System in Pellagra, THE ARCHIVES INT. MED., 1913, xi, 565.



F. B. M., white, male, aged 21, no occupation. Anamnesis obtained from the father, stepmother, sister and the patient. The mother died in all probability of pellagra seventeen years ago, although the diagnosis was not made at the time. Her illness is described as resembling in all particulars that of the patient as regards eruption on the hands, stomatitis and dysentery, except that it was more severe. The mother was nervous but there is no other history of importance.

The patient was always healthy and thought to be of average brightness. He had never been very enthusiastic about games and always preferred to play with children younger than himself. He was well liked, but had no confidants and kept much to himself; never cared to go out to parties, stayed much around home, and did not mix with members of the opposite sex. He was never a leader; did not read much and although he took pleasure in driving an automobile and caring for it, he seems to have spent much of his spare time loafing around the house. He has formed no definite plans or ambitions and seems to have taken it for granted that he will enter his father's business of lumber merchant. He has never caused any anxiety by getting into mischief and has been thought above the average in regard to morality. Thus the striking features of his make-up are chiefly negative and there is a lack of the push, activity and mischief of the average healthy boy.

In the summer of 1910 he suffered with an attack of malaria which was not very severe and from which he made a good recovery.

In March, 1911, there developed an erythema of the backs of the hands with some malaise which was recognized as *pellagra*. This attack was mild and disappeared in two or three weeks, but on his return to school it was noticed that he did not take as much interest as before. He wished to leave and fell behind so that his younger sister caught up and eventually passed him. He seemed to be unable to get his lessons, loafed around more and was even more retiring than formerly.

In the summer of 1911 he delivered papers for a newsdealer for a few days but then gave it up. While on his rounds he had a peculiar "spell" and had some ten or twelve of these between that time and October, 1912. As these attacks are said to be all alike it will suffice to describe one.

Spells: The onset is more or less abrupt and apparently most often during walking. The first manifestation is a sense of "drawing of the left side of the body," which seems to pull him over backwards and to the left. On some occasions he has been able to reach some support but generally he has fallen. His legs rapidly become stiff, weak and numb and for a while he cannot move them at all. There is no pain, dizziness or loss of consciousness according to the patient. The sister, however, stated that he had once been brought home unconscious in one of these spells. The patient recalls the incident and has apparently a clear recollection of it, so that it is at least doubtful whether he has ever lost consciousness. In an attack seen by the father he remained clear throughout. The paralysis gradually passes off and he is quite all right again in about fifteen to twenty minutes after the onset. In the attack observed by the father in June, 1912, while out in the woods he was able to walk back to camp at the end of twenty minutes, a distance of one and one-half miles.

There has never been any convulsive movement nor loss of sphincter control and he has seemed to recover fully afterwards.

In March, 1912, there was a second and more severe attack of *pellagra*. Following this he became listless, wanted to leave school and said that he could not keep his mind on his books. He did not seem depressed, but merely loafed on the porch or about the house. About the end of June he showed more definite evidence of insanity and began to express such notions as that everyone was watching them, the house was to be burned and they were to be shot. He did not react much to these thoughts and showed no sign of fear, but he did ask for his gun, which had been removed by his relatives, and once spoke to a policeman asking him to be on the watch for these people. He

wandered aimlessly about the house peering into corners and rummaging in drawers and had to be watched to prevent him from going away from the house. For a long time he carried a woolly rug around with him, offering no explanation for so doing. He seemed to take little notice of anything and was often very "obstinate." For a time he was entirely mute and refused food and medicine. He would object to getting into a bath and, once in, would refuse to come out, although he was never violent. Sense-falsifications were probably present. He would stop as if listening and mutter to himself and spoke of electricity and automobiles in his back.

He seems to have slowly become worse until October, 1912, when he was committed to the Columbia State Hospital. At this time it was noticed that he was weak in his legs and hands and required supporting to walk at all. This was, however, attributed to disuse and was not considered seriously.

It was impossible to determine the exact relation between the pellagra and the mental disturbance. The listlessness and loss of interest appeared in marked form soon after the appearance of the eruption on the hands, but this was entirely gone when he went to Columbia. It seemed probable that the diarrhea and stomatitis, which were present in March, had disappeared before July.

At Columbia the patient remained in bed with apparent indifference to his surroundings, but without active symptoms of any kind. Slowly he began to improve, both as regards interest in his environment and home, in his walking and the use of his hands, which were at first practically in abeyance. He was discharged as recovered July 17, 1913.

When examined the day after his return home the following facts were noted: A tall, muscular lad with an apparent age of not more than 17, although he was actually 21. There was little hair on the face, although it was normally present elsewhere on the body. The ears were large, irregular and asymmetrical. Genitalia well developed.

The gait was markedly spastic and he used a cane in walking. The feet showed a high arch. The knee- and ankle-jerks were markedly and equally exaggerated and a few clonic jerks, not sustained, were obtained at both ankles. Both plantar reflexes were of extensor type. The small muscles of the hands were much atrophied, with a characteristic *main en griffe*. The forearm muscles were small and power was much diminished, the wrists showing definite extension when an attempt was made to grip firmly. The grips were both feeble. No atrophy was detected elsewhere. Electrical examination was impossible owing to the lack of apparatus. The abdominal muscles were of good power and the epigastric and abdominal skin reflexes were present.

The only sensory disturbance discovered was a hypalgesia, not by any means complete, in the region of the first dorsal root distribution on the left forearm. No incoordination was detected.

A fine lateral nystagmus was present on extreme deviation of the eyes, especially when they were rotated to the left. No other ocular disturbances. Fundi healthy. The tongue deviated slightly towards the left when protruded, but there was no obvious loss of power in any movement and no defect in speech or swallowing. The facial movements were normal.

Bladder disturbance was at first entirely denied, but in reply to a leading question it was learned that there had developed some hesitation in starting the flow of urine.

The picture is thus not very clear or characteristic, but it was thought that the condition was probably one of syringomyelia and that the transient "attacks" of paraplegia might be due to minute hemorrhages or other vascular disturbance in the growth. Although it is said that he recovered perfectly from these attacks, it should be noted that the onset of the spasticity and atrophy of muscle were not noticed until they were severe and that the onset was quite possibly very insidious.

Katamnesis: With regard to the evidences of mental disorder, the patient simply denied most of them although he claimed to have been entirely clear

throughout. He admitted that he had been "out of his head" for the first period of his residence at Columbia, but attributed this to drugs and hypodermics. (The only drugs used were simple tonics.) He denied sense-falsifications except that he had had shocks "like electricity" in his back; denied that he had ever thought the house was to be burned or that people were watching the house. He would not meet or talk to people because he was afraid he might have one of his "attacks," of which he was ashamed. His memory for the events of the period of psychosis is apparently good and he gave a good account of his trip to Columbia.

He talked freely and answered questions without apparent evasion, but volunteered little and was not deeply concerned. His father considered him entirely recovered and attributed the somewhat listless attitude and poor interest to the weakness and disability resulting from the nervous lesion.

In spite of the close relation in point of time between the onset of the nervous symptoms and the attack of pellagra, one can hardly doubt that here the latter acted merely as a precipitating factor, both with regard to the psychosis and the nervous disease. As is well known, syringomyelic conditions are occasionally discovered at autopsy which have apparently caused no symptoms during life; also, it is not uncommon for the clinical manifestations to appear following some infectious fever in individuals who have previously been considered normal. The same is also true for other diseases belonging to this group of congenital anomaly, so that even if the suggestion that this is a case of syringomyelia is not correct the argument will still hold. The same explanation in all probability applies to the case published in England by Box<sup>9</sup> with a histological study by Mott.<sup>10</sup>

The occurrence of such cases as this is a further argument in favor of the suggestions which have been made in discussing the mental disorders, that faulty nervous organization seems for some reason to be associated with a predisposition to pellagra.

In closing this chapter reference may be made to the frequency with which manifestations appeared to point to especial involvement of the vestibular apparatus. This has been recorded before, but seemed to be especially prominent in the more severe forms of the disease observed in Spartanburg. Vertigo, often extremely annoying, at times constituted the main complaint of the patient. It was often sudden in onset and would result in falling, sometimes with vomiting. In most cases this dizziness would appear only when the patient was up and walking about, but in some it was present at times even when lying down. It was usually associated with more or less severe tinnitus and less frequently with a sense of pressure on the head. None of these attacks was actually observed. Among the eighteen severe cases in

9. Box, Charles R., and Mott, F. W.: *Trans. Soc. Trop. Med. and Hyg.*, 1913, vi, 149; *Brit. Med. Jour.*, July 5, 1913, p. 2.

10. Mott, F. W.: *Trans. Soc. Trop. Med. and Hyg.*, 1913, vi, 157; *Brit. Med. Jour.*, July 5, 1913, p. 4.

the Good Samaritan Hospital, this syndrome was more or less prominent in six.

#### SUMMARY AND CONCLUSIONS

1. Mental disturbance occurs in about 40 per cent. of all cases of pellagra. Such disturbances are more frequent with repeated attacks. Children are practically exempt. They are most common in men between 21 and 40, and women about 41 to 60.

2. About 95 per cent. of the mental disorders are the direct result of the pellagrous intoxication, and although the mortality in such cases is much higher than in cases without such disorder, yet the mental disturbance will fully recover if the patient survives. They correspond to similar disturbances in other somatic diseases and in such case are often described as not "insanity." The remaining 5 per cent. are examples of mental disorder primarily dependent on the individual's make-up, or else are merely concomitant.

3. Faulty nervous organization, including inadequate mental adaptability, seems to be associated with a predisposition to pellagra. This seems to afford the most satisfactory, even if only partial, explanation of the extraordinary frequency of pellagra arising among the insane, the increased frequency of functional psychoses and psychoneuroses and of nervous disease of the congenital anomaly type among pellagrins as compared with more normal individuals.

4. Chronic "insanity" due strictly to pellagrous intoxication, if it occurs, is rare.

5. Chronic nervous disease as the result of pellagra, if it occurs, is exceptional.

## FURTHER OBSERVATIONS ON THE BLOOD-COUNT IN PELLAGRA \*

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In a previous article<sup>1</sup> one of us summarized the more important changes that occur in the blood-count in pellagra. In the present communication we desire to record briefly our observations on another series of pellagrins, all of whom resided in, or adjacent to, Spartanburg County, South Carolina, in which locality the Thompson-McFadden Pellagra Commission has been investigating the disease. The data included in this report were obtained from patients examined during the summer and early fall months of 1913, when many new cases of pellagra were seen, as well as a large number of patients who had had one or more attacks of the disease. The information derived from this study confirms and amplifies the work of the commission carried on along the same lines in 1912. In the investigations of 1913 more particular attention was given to the relationship (if any) existing between the total leukocyte and differential counts, especially in the primary acute attacks of the disease. It was our main intention, however, to examine a fairly large and representative series of cases from the standpoint of the differential count, even in the absence of the correlated total leukocyte count. A few confirmatory observations were also made on the hemoglobin percentage and number of red corpuscles. The actual technic employed was essentially the same as detailed in the former paper, and was such as to insure consistent results with a minimal error.

In the accompanying table the differential leukocyte count is given on a series of forty-six pellagrins, together with the total leukocyte count when this was made, and also a few remarks with regard to the incidence of the attack, its nature (whether mild or severe), and the probable duration of the attack. Inspection of the table discloses the fact that lymphocytosis is the predominant feature in the majority of cases. In this connection it might be said that a few observations made on non-pellagrins in regions where pellagra was endemic revealed a moderate relative lymphocytosis, incidental, in all probability, to a poor state of general health, or to some mild gastro-intestinal disturbance.

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1. Hillman: *Am. Jour. Med. Sc.*, 1913, cxiv, 507.

TABLE GIVING DATA CONCERNING BLOOD-COUNT OF PELLAGRINS

Name	Case No.	Sex	Age	Polynuclears	Lymphocytes	Large Monos.	Transitionals	Eosinophils	Basophils	Total Leukocytes	Nature and Duration of Attack
Q. J. F. ....	629	M	51	58.00	38.40	1.20	0.0	2.00	0.10	6,700	First attack, mild; six months.
D. W. ....	630	M	32	68.80	18.80	3.70	2.80	3.15	0.25	1,300	Recurrent attack, chronic; six months.
M. M. ....	628	F	30	72.80	18.40	1.00	1.40	3.10	0.20	10,000	First attack, severe; six weeks.
H. W. ....	518	F	40	49.75	40.25	2.50	1.00	0.50	0.0	6,650	First attack, severe, chronic; three months.
E. H. ....	583	F	38	64.20	25.40	1.40	0.80	1.20	0.0	7,200	Recurrent attack, chronic.
C. C. C. ....	583	M	43	78.75	16.25	2.25	2.40	0.25	0.0	6,000	Recurrent attack, chronic; two months.
S. J. H. ....	511	M	62	70.80	22.00	2.60	1.00	3.00	0.0	.....	Recurrent attack, chronic; four months, recovery.
S. M. ....	584	F	10	64.20	32.40	1.00	0.80	0.60	0.0	.....	Recurrent attack, chronic; three months, recovery.
E. S. ....	584	F	54	51.60	45.00	1.00	0.40	1.40	0.0	.....	Recurrent attack, chronic; six weeks, recovery.
S. R. M. ....	510	M	19	68.00	25.75	3.50	1.00	1.75	0.0	6,950	First attack, chronic; two months, recovery.
M. W. M. ....	688	M	52	53.40	38.40	3.20	0.60	4.40	0.0	8,800	First attack, chronic, two months.
B. S. A. ....	53	F	44	55.80	35.00	0.80	0.80	7.60	0.0	.....	Recurrent attack, chronic, mild, recovery.
E. S. ....	570	F	38	43.00	54.85	0.85	0.0	1.20	0.0	6,000	First attack, subacute; one month, recovery.
S. ....	509	M	48	63.75	32.50	0.50	0.25	2.00	0.0	8,200	Recurrent attack, chronic; one month, died.
S. ....	509	M	48	67.50	25.75	4.00	0.0	2.50	0.25	.....	Recurrent attack, chronic; died.
S. W. H. ....	506	M	33	68.25	25.00	1.00	0.00	5.50	0.25	.....	Recurrent attack, chronic; two months.
S. L. ....	76	F	35	58.80	38.00	0.80	0.30	2.00	0.0	7,500	Recurrent attack, chronic; recovery.
A. V. ....	506	M	13	65.00	30.25	1.50	1.00	2.00	0.25	.....	First attack, mild; recovery.
W. C. C. ....	501	M	32	50.25	31.25	3.75	2.00	2.75	1.00	.....	First attack, subacute; recovery.
C. D. E. ....	255	M	25	56.67	32.67	3.33	0.67	6.66	0.0	8,250	Recurrent attack, acute; two weeks.
F. L. T. ....	523	M	35	51.00	31.80	7.20	1.40	4.80	0.60	8,800	Recurrent attack, chronic.
T. M. P. ....	139	M	38	18.40	46.80	0.80	2.00	1.60	0.40	.....	First attack, chronic; mild, recovery.
C. M. ....	387	F	35	67.00	29.30	1.00	1.50	1.20	0.0	.....	Recurrent attack, acute; three weeks, died.
W. C. J. ....	526	M	19	73.80	22.00	1.00	2.00	1.20	0.0	7,150	First attack, acute; two weeks.
W. C. J. ....	526	M	19	38.00	59.30	1.10	0.60	1.00	0.0	6,700	First attack, subacute.
M. E. C. ....	508	M	48	52.50	39.00	2.50	0.0	4.50	1.50	6,000	Recurrent attack, acute; five weeks, died.
W. M. ....	508	F	12	53.60	34.20	1.80	1.40	8.80	0.20	8,800	First attack, chronic; five weeks, recovery.
R. W. C. ....	502	M	26	73.00	18.90	1.50	2.00	1.10	0.50	8,750	Recurrent attack, chronic.
S. ....	508	F	20	70.00	24.00	2.00	1.00	2.60	0.40	.....	Recurrent attack, acute; died.
S. S. H. ....	144	F	33	51.20	37.80	2.60	3.00	5.60	0.40	.....	Recurrent attack, acute.
M. C. E. ....	504	F	17	50.00	33.40	2.20	2.20	2.80	0.40	10,150	First attack, acute; one week.
S. ....	503	M	35	55.00	43.00	1.35	0.67	0.0	0.0	9,800	First attack, acute.
A. J. A. ....	505	M	35	45.70	49.30	2.40	0.30	2.30	0.0	7,550	First attack, acute; four weeks.
S. E. ....	707	M	14	42.00	47.00	4.50	1.50	5.50	1.50	9,800	Recurrent attack, chronic; one month.
B. J. ....	16	F	25	54.75	34.50	2.00	1.75	3.75	1.25	6,650	First attack, subacute; two months.
H. E. ....	...	F	35	61.25	33.50	2.75	1.00	1.00	0.50	.....	Recurrent attack, chronic.
F. S. ....	586	F	54	45.50	49.00	0.50	1.50	3.00	0.50	.....	Recurrent attack, subacute.
W. R. G. ....	658	F	37	67.50	26.00	3.00	2.50	0.50	0.50	.....	First attack, acute; two weeks.
E. W. ....	569	M	10	50.50	43.50	2.00	0.25	3.50	0.25	9,800	Recurrent attack, chronic; mild.
H. M. ....	703	F	16	66.75	22.50	3.00	1.00	3.75	0.0	8,000	First attack, acute; two weeks.
R. L. L. ....	703	M	30	44.25	31.50	2.25	0.50	1.50	0.0	.....	First attack, subacute; two months.
D. A. ....	552	F	21	61.50	32.75	3.25	1.25	1.25	0.0	.....	Recurrent attack, chronic.
H. D. ....	572	F	32	42.00	57.00	0.50	0.0	0.25	0.25	8,000	First attack, chronic; mild.
D. ....	575	F	30	51.00	40.50	5.50	1.0	1.25	0.75	6,500	First attack, chronic; two months.
G. E. ....	501	F	34	58.00	35.00	1.00	0.5	5.00	0.50	.....	Recurrent, chronic; six weeks, severe.
E. ....	108	F	54	64.75	32.50	1.00	0.25	0.25	0.25	7,100	
Averages ....				58.87	34.57	2.25	1.13	2.86	0.55		



In cases showing a decided lymphocytosis, the total number of leukocytes was practically normal or only slightly below normal in a few instances. Marked and persistent leukopenia does not seem to be a feature of this disease. As far as we were able to determine from the cases studied, there appears to be no definite relation between the degree of lymphocytosis and the severity or chronicity of the attack. The small lymphocyte with relatively little cytoplasm is the most common type of lymphocyte in pellagrous blood.

In the few patients examined during the first stages of an acute attack, a tendency was noted toward a slight rise in the leukocytes to maximum normal or a trifle beyond, but in no instance was a pronounced leukocytosis found. The differential count on these cases did not exhibit a polynucleosis, and in only one case of acute severe pellagra were the polynuclears over 70 per cent. A rise in polynuclears was recorded in a few recurrent chronic cases, due most likely to complicating factors.

It has been mentioned by some workers on pellagra that the so-called large mononuclear leukocyte is relatively increased. Our observations would not tend to substantiate this finding as a constant feature, although in a few cases a slight rise in this type of cell was noted.

The eosinophils varied considerably, as may be seen from the table. A very moderate eosinophilia was found in occasional cases, but to state that eosinophilia is characteristic of pellagra would not be justified from a study of this analysis. The prevalence in the South of hookworm infection and other forms of intestinal parasitism capable of causing an eosinophilia, is a factor to be considered in interpreting slight fluctuations in the number of eosinophilic leukocytes.

With regard to the changes in the amount of hemoglobin and in the number of red corpuscles, it might be said that nothing further was detected other than a mild degree of secondary anemia which has been already noted in the first report. This anemia is not at all constant or characteristic of the disease. Cases of decided anemia occurred for the most part in patients afflicted with some associated condition to which the anemia was probably referable rather than to the pellagra *per se*.

# STREPTOCOCCUS VIRIDANS IN ITS RELATION TO INFECTIONS OF THE UPPER RESPIRA- TORY TRACT\*

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During the past decade numerous efforts have been made to devise a satisfactory classification of streptococci, most of them being based on the carbohydrate fermentation test. The most notable of the studies have been those of Gordon,<sup>1</sup> S. Andrewes and Horder,<sup>2</sup> Winslow,<sup>3</sup> and Floyd and Wolbach.<sup>4</sup> The reliability of the fermentation test has been questioned by Walker<sup>5</sup> and others. Schottmueller's<sup>6</sup> classification of streptococci, based on the appearance of the colonies on blood-agar, is at present perhaps the most practical, if not the most accurate classification of these bacteria. He divides them as follows:

1. *Streptococcus haemolyticus* (*longus*, *pyogenes*), which on blood-agar produces a clear zone of hemolysis about the colony; morphologically, it appears in chains of round or slightly oval cocci; this is the type almost constantly found in erysipelas, complications of scarlet fever and various suppurative processes of streptococcus origin.

2. *Streptococcus viridans* (*mitior*), which on blood-agar develops as a very small gray colony, surrounded by a zone of green; in smears the cocci are seen in pairs which resemble pneumococci, or in short and long chains of cocci, arranged in pairs. *Streptococcus viridans* is usually without capsule; it occurs chiefly in infections of endothelial and mucous surfaces.

3. *Streptococcus mucosus*, the colonies of which appear on blood-agar as delicate, colorless, transparent, glistening drops of a mucoid consistency; microscopically, it is composed of chains of diplococci, surrounded by a thick capsule which shows no indentation between the pairs.

Schottmueller's work has been followed by a number of similar studies in which the reaction on blood has been used as a basis for classification. Most of these investigators find that, clinically, the

\* Submitted for publication July 16, 1914.

\* From the Medical Clinic of the Presbyterian Hospital.

1. Gordon: Lancet, London, 1905, ii, 1400.

2. Andrewes and Horder: Lancet, London, 1906, clxxi, 708, 775, 852.

3. Winslow: Jour. Infect. Dis., 1912, x, 73.

4. Floyd and Wolbach: Jour. Med. Research, 1914, xxix, 493.

5. Walker: Jour. Path. and Bacteriol., 1910, xv.

6. Schottmueller: München. med. Wehnschr., 1903, li, 849, 909.

*Streptococcus haemolyticus* and *Streptococcus viridans* produce more or less characteristic lesions, the former being associated with suppurative or phlegmonous inflammation, the latter usually with milder catarrhal processes.

During the last two years I have been making a study of the bacteriology of infections of the upper respiratory tract, with special reference to the rôle played by *Streptococcus viridans* in these cases. The object of the investigation has been to determine:

1. The incidence of *Streptococcus viridans* in infections of the various parts of the upper air passages and their adnexa.
2. The clinical features of those infections in which *Streptococcus viridans* was the predominant organism.
3. The relation of such infections to arthritis, endocarditis and other systemic disorders.
4. The value of autogenous vaccines in their treatment and prevention.

More than a hundred cases have been studied, but for various reasons only eighty-nine have been included in the present report. The material for this study has been obtained for the most part from the medical clinic of the Presbyterian Hospital. A few cases from private practice have also been added.

#### TECHNIC

Without exception, the original cultures have been taken on glucose-blood-agar plates (in all cases human blood) defibrinated by sodium citrate or by shaking with glass beads. The agar was melted and one part of defibrinated blood added to two or three parts of agar. After the plates had hardened, the material to be examined was smeared over several of these (usually three) with sterile glass rods. This medium possesses the double advantage of being suitable for all the bacteria occurring in these parts and of furnishing a basis for the classification of streptococci according to Schottmueller's method. The differentiation of the green from the hemolytic colonies was much easier when the plates were a deep pink rather than red. This color was obtained by having the plates not too thick and by using blood slightly diluted with serum or salt solution. The blood used was always comparatively fresh and free from spontaneous hemolysis. It was found that blood which had remained in the ice-box for ten days or two weeks was unreliable. In old blood the cells become fragile and many strains of streptococci will produce hemolysis in it which fail to do so in fresh blood. In nearly every case smears were made at the time the cultures were taken and stained with methylene blue, Hiss' capsule stain and the Gram stain. The method of taking the

cultures will be described with each particular group of cases. A special effort was made in this study to determine the *predominating* organism; while pure cultures were rarely obtained, it was found that with careful technic one, or at most two, organisms usually far outnumbered any others that might be present and in so far as they predominated could be looked on as the probable exciting agents in the infection. In those few cases in which pure cultures were obtained there was no doubt as to the character of the infection. In the others, the presumption was, of course, in favor of the predominant organism, but one could no longer be sure that the infection was a pure one.

#### THE STREPTOCOCCUS VIRIDANS

Before proceeding to a consideration of the problems mentioned above, a brief description of the *Streptococcus viridans* might not be out of place. *Streptococcus viridans* in a typical form is a very small Gram-positive diplococcus which grows in pairs or short chains. The arrangement of the cocci in pairs is rather characteristic. It is usually described as having no capsule. The individual cocci are oblong and often definitely lanceolate. The chains are sometimes quite long, especially in liquid mediums, in which they may extend across the entire field of the microscope, but short chains are more typical. On glucose-blood-agar colonies on the surface develop slowly as minute round gray dots, with a narrow halo of green. If the blood-agar is thick and contains considerable blood, the colony takes on a brownish tinge. Deep colonies are round or fusiform and light green with darker centers. If old blood has been used, a certain amount of hemolysis may occur, but even then the green color survives. The pneumococcus also has a green colony on blood-agar, but it is larger and flatter, usually umbilicated and produces more green than the *Streptococcus viridans*. On plain or ascitic agar the *Streptococcus viridans* forms small gray colonies which may show (1) adherence to the medium and (2) considerable variations in size, so that one often suspects the culture of being contaminated. On ascitic agar there is occasionally some precipitation of the albumin, but never so marked as in the case of *Streptococcus haemolyticus*. The growth on ascitic agar is more luxuriant than on plain agar; on plain or ascitic broth there is usually produced a slight turbidity with a flocculent or granular sediment in the bottom of the tube; litmus milk is coagulated; inulin may or may not be coagulated, usually not. *Streptococcus viridans* is not soluble in bile or bile salts.

*Variations.*—The question as to whether the *Streptococcus viridans* is a pure type or merely an attenuated variant of the pneumococcus, is still an open question, with the evidence at present in favor of the

latter. The typical *Streptococcus viridans* is very small, but larger forms are often seen. The colony varies in size with that of the coccus. Short chains are more characteristic than long ones, but long chains do frequently occur. Small capsules are sometimes seen, in fresh smears particularly, after passage of the organism through animals. On culture mediums the variations are not marked. Strains are encountered which on the one hand approach the *Streptococcus haemolyticus*, forming no green and showing a slight tendency toward hemolysis; on the other hand, there are forms which resemble the pneumococcus, with colonies which are larger than that of the typical *Streptococcus viridans* and surrounded by a broader zone of green. In some cases the distinction from the pneumococcus is very hard to make. I have used the bile test as a final criterion. Inulin is fairly reliable, but there are a certain number of *Streptococcus viridans* cultures which will coagulate inulin. By repeated passage through animals Rosenow<sup>7</sup> was able to coagulate inulin with all his strains of *Streptococcus viridans*. He inferred from this and other mutations that the *Streptococcus viridans* was a modified pneumococcus. More recently Rosenow<sup>8</sup> has reported that by subjecting the organism to various modifications in environment he has succeeded in transmuting streptococci into typical pneumococci and vice versa. The significance of this work will be referred to later.

*Virulence.*—*Streptococcus viridans* is an organism of very low virulence for animals and rarely produces fatal infections in human beings. Of all the types in the streptococcus-pneumococcus group it approaches the nearest to being a saprophyte. This is particularly true of those growing in the normal buccal cavity. Davis<sup>9</sup> found that the typical *Streptococcus viridans* rarely produced arthritis in rabbits when injected intravenously. On the other hand, he and Rosenow<sup>10</sup> both found that experimental endocarditis could be produced in nearly every instance by inoculation with organisms of the *viridans* type. The organisms which Rosenow isolated from the joints in acute rheumatism he divided into three groups:

1. Diplococci which produce green on blood-agar.
2. Diplococci which produce slight hemolysis on blood-agar.
3. Diplococci which have no effect on blood-agar.

All these groups produce arthritis, endocarditis and pericarditis when injected into rabbits. The second group may also cause a myositis.

7. Rosenow, E. C.: Jour. Infect. Dis., 1910, vii, 411.

8. Rosenow, E. C.: Jour. Infect. Dis., 1914, xiv, 1.

9. Davis, D. J.: Jour. Infect. Dis., 1913, xii, 386.

10. Rosenow, E. C.: Jour. Infect. Dis., 1914, xiv, 61.

*Immune Bodies.*—Rosenow<sup>7</sup> has shown that the *Streptococcus viridans* produces specific agglutinins in chronic infectious endocarditis. The same investigator has studied the opsonins in chronic endocarditis of *Streptococcus viridans* origin. He has found that the opsonic index varies considerably at different periods of the disease and that embolism and other intercurrent processes in endocarditis are associated with a definite lowering of the destructive power of the patient's blood. Hastings<sup>11</sup> has recently employed complement-fixation tests for the diagnosis of *Streptococcus viridans* infections, particularly those of the joints. Rosenow and Davis have both succeeded in sensitizing guinea-pigs to *Streptococcus viridans*. Davis also found that animals sensitized to *Streptococcus haemolyticus* were not shocked by *Streptococcus viridans*.

*Incidence of Streptococcus Viridans.*—*Streptococcus viridans* has come to be associated in the minds of many almost exclusively with chronic infectious endocarditis. While it is the most frequent exciting agent in this disease, it should more properly be thought of as an inhabitant of the mouth and upper respiratory tract. It can be isolated from practically every normal mouth and throat. The importance of the streptococcus in infections of the upper respiratory tract has long been recognized, but comparatively little has been done to distinguish the various types from one another. *Streptococcus haemolyticus*, *Streptococcus viridans*, *Streptococcus mucosus* and the pneumococcus may all be found in healthy mouths, the *viridans* being usually the most abundant. In spite of this fact, however, most investigators of the bacteriology of the infections of the upper respiratory tract have been content to throw all streptococcus infections into one group, so that comparatively little is known of the relative importance of the different types in these infections. Schottmueller in his original article found *Streptococcus viridans* in tonsillitis, conjunctivitis, acute and chronic rhinitis, otitis media, empyema, pericarditis, lung abscess, endocarditis, acute enteritis and other abdominal inflammatory conditions; and recent studies of Camac,<sup>12</sup> Billings<sup>13</sup> and others on the relation of oral sepsis to chronic arthritis and the demonstration by Rosenow of *Streptococcus viridans* in the joints of rheumatic fever indicate what an important rôle this organism and its variants play in infections of the mucous and serous surfaces.

In the eighty-nine cases of infection of the upper respiratory tract which constitute the present bacteriological study, fifty, or 56.2 per

11. Hastings, T. W.: Jour. Exper. Med., 1914, xx, 52, 72.

12. Camac: Am. Jour. Med. Sc., 1914, cxlvii, 186.

13. Billings, Frank: Chronic Focal Infections and Their Etiologic Relations to Arthritis and Nephritis, THE ARCHIVES INT. MED., 1912, ix, 484.



cent., have shown a predominance of *Streptococcus viridans* on blood-agar plates. It seems rational in an investigation of this nature, in which, even with scrupulous technic, colonies of several species are often found on the plate, to attribute chief importance to the organism or organisms which are most largely represented. This is particularly true when the bacteria in question are hard to cultivate. For example, it would be much more significant if a plate showed 90 per cent. of its colonies to be *Bacillus influenzae* or *Streptococcus viridans*, than it would be if the plate were overgrown with *Bacillus proteus* or *Staphylococcus albus*. In the latter instance one would hesitate about making a positive bacteriological diagnosis, whereas in the former case, he could feel fairly sure that the specific organism had been discovered.

In the present study I have given especial attention to the number of colonies of each species present. My results therefore can hardly be compared with those of previous investigators who have usually set down merely the names of the organisms present without any reference to which were predominant.

By referring to the table of cases it will be seen that the *Streptococcus viridans* has been predominant in more than one-half of the cases studied. It has also been present, but not predominant, in a good many others. Next to the *Streptococcus viridans* in frequency comes the closely related pneumococcus which, including *Streptococcus mucosus*, was predominant in eighteen cases, or 20.2 per cent. of the series. The third in order of frequency was the *Streptococcus haemolyticus*, which was predominant in six cases (6.7 per cent.). These three organisms, therefore, were apparently the most active factor in about 83 per cent. of the cases studied. The remaining 17 per cent. was divided between *Bacillus influenzae*, *Micrococcus catarrhalis*, Friedländer's bacillus, *Bacillus septus*, *Staphylococcus aureus*, *Micrococcus paratetrageus*, and *Staphylococcus albus* and *citreus*. *Bacillus coli* and *Bacillus proteus* were never predominant. Some form of staphylococcus was encountered in almost every case, but only in a few instances was it predominant. The staphylococci appear to play a very insignificant rôle in infections of the upper respiratory tract.

#### STREPTOCOCCUS VIRIDANS IN INFECTIONS OF THE TONSILS

The streptococcus is by far the commonest micro-organism found in infected tonsils, both acute and chronic. This fact is so widely known that no reference to the literature is necessary. The distinction, however, between the *viridans* and other types of streptococci has not been usually made. Schottmueller,<sup>6</sup> Ruediger<sup>14</sup> and others have observed that the *Streptococcus haemolyticus* is usually found on the

14. Ruediger: Jour. Infect. Dis., 1906, iii, 755.

tonsils in scarlet fever. Streit,<sup>15</sup> in a recent study, found the *Streptococcus haemolyticus* in forty-nine out of fifty-six cases of tonsillitis and peritonsillar abscess. Davis<sup>16</sup> has recently studied the bacteriology of tonsillitis, particularly in relation to chronic rheumatic and renal disease. He examined extirpated tonsils from a large series of cases, mostly of arthritis, heart disease and chronic nephritis, and found that the *Streptococcus haemolyticus* was present in a large percentage of

Type of Infection	No. of Cases Studied	Strept. viridans Predominant	Other Organisms Predominant								
			Pneumococcus	Strept. haemolyt.	Strept. mucosus	Staph. aureus	Staph. albus	B. Influenzae	B. Friedlander	Mic. catarrh.	B. sept.
Acute tonsillitis .....	7	4	1	2	.....	.....	.....	.....	.....	.....	..
Acute tonsillitis associated with rheumatic fever .....	5	5	.....	.....	.....	.....	.....	.....	.....	.....	..
Chronic tonsillitis .....	5	2	1	1	.....	.....	1	.....	.....	.....	..
Chronic tonsillitis associated with infectious endocarditis .....	2	2	.....	.....	.....	.....	.....	.....	.....	.....	..
Chronic tonsillitis associated with chronic arthritis .....	4	3	.....	1	.....	.....	.....	.....	.....	.....	..
Pyorrhea alveolaris .....	5	5	.....	.....	.....	.....	.....	.....	.....	.....	..
Alveolar abscess .....	2	2	.....	.....	.....	.....	.....	.....	.....	.....	..
Pyorrhea associated with acute arthritis .....	1	1	.....	.....	.....	.....	.....	.....	.....	.....	..
Pyorrhea associated with chronic arthritis .....	4	4	.....	.....	.....	.....	.....	.....	.....	.....	..
Pyorrhea associated with chronic nephritis .....	2	2	.....	.....	.....	.....	.....	.....	.....	.....	..
Alveolar abscess associated with infectious endocarditis .....	1	1	.....	.....	.....	.....	.....	.....	.....	.....	..
Acute coryza with pharyngitis .....	8	5	2	.....	.....	.....	.....	.....	.....	.....	1
Infections of the accessory sinuses .....	8	3	3	.....	.....	.....	.....	1	1	.....	1
Infections of the ethmoid cells .....	4	.....	1	.....	.....	1	.....	.....	1	.....	..
Chronic dacryocystitis .....	1	1	.....	.....	.....	.....	.....	.....	.....	.....	..
Otitis media, acute .....	5	1	1	2	1	.....	.....	.....	.....	.....	..
Otitis media, chronic .....	2	.....	.....	.....	.....	2	.....	.....	.....	.....	..
Acute laryngitis .....	1	.....	1	.....	.....	.....	.....	.....	.....	.....	..
Acute bronchitis .....	8	4	3	.....	.....	.....	.....	1	.....	.....	..
Chronic bronchitis .....	6	4	1	.....	.....	.....	.....	1	.....	.....	..
Chronic pharyngitis .....	1	.....	1	.....	.....	.....	.....	.....	.....	.....	..
Chronic rhinitis .....	3	.....	.....	.....	.....	.....	.....	.....	1	1	1
Normal throat .....	4	1	2	.....	.....	1	.....	.....	.....	1	..
Total .....	89	50	17	6	1	3	1	3	3	2	3

them. In a few cases *Streptococcus viridans* was the predominant organism. His cultures were taken from deep in the tonsillar crypts. My own studies of the tonsillar flora have been confined to cultures taken from that organ in situ. Cultures were obtained as follows: The tonsil was wiped off with a sterile swab, and a sterile platinum

15. Streit: Arch. f. Laryngol. u. Rhinol., 1913, xxvii, 393.

16. Davis, D. J.: Bacteriological and Experimental Observations of Focal Infections, THE ARCHIVES INT. MED., 1912, ix, 505.

wire inserted as deep as possible into one of the crypts. The material removed was then spread over the surface of several blood-agar plates with a sterile glass rod. By this method colonies on the second or third plate were always sufficiently well separated for study. Smears were also made and stained in the usual way. The plates were examined after incubation at 37.5 C. (99.5 F.) for twenty-four hours and again after forty-eight hours, the predominating colony or colonies determined and the various types subcultured for further study.

I have examined the tonsils of twenty-three patients with more or less evidence of tonsillar disease. In sixteen of these *Streptococcus viridans* has been present in large numbers, sometimes in pure culture. In the remaining seven cases the pneumococcus or *Streptococcus haemolyticus* predominated, except in one instance in which *Staphylococcus albus* was found in almost pure culture.

#### *Acute Tonsillitis.*

The cases of tonsillitis, both acute and chronic, in which *Streptococcus viridans* has been the predominant organism, have been of a mild, or only moderately severe type. The *Streptococcus haemolyticus* is usually found with the tonsillitis of scarlet fever and peritonsillar abscess. I have seen several quite severe cases of tonsillitis from which pure cultures of the pneumococcus were obtained. Most cases of mild tonsillitis are probably due to *Streptococcus viridans*, but the clinical picture is certainly not characteristic enough to allow of a bacteriological diagnosis without a bacteriological examination.

It should be added that the smears made in these cases corresponded with the cultures, showing pus cells and diplococci in short chains.

In the one case of this group in which autogenous *Streptococcus viridans* vaccine was used the response was immediate. A tenacious membrane which had resisted local treatment for ten days disappeared within twenty-four hours after vaccination, and the patient made a rapid recovery.

#### *Acute Tonsillitis Associated with Rheumatic Fever*

In spite of the well-known association of tonsillitis with rheumatic fever, I know of no careful or extensive study of the bacteriology of the tonsil in this connection. My own series consists of only five cases. Cultures from the crypts of the tonsils in all of these showed *Streptococcus viridans* as the predominant organism. In one case it was present in pure growth.

Unfortunately, no cultures were made from the joints in any of these cases. Rosenow has recently cultivated from the joints in rheumatic fever streptococci which produce green on blood-agar and "after

prolonged cultivation come to resemble *Streptococcus viridans* in morphology, in cultural and pathogenic qualities." Rosenow's organism is probably identical with Poynton and Pane's<sup>17</sup> *Streptococcus rheumaticus*. In view of the widely accepted theory that the tonsil is the portal of entry for the organism of rheumatic fever, it is interesting to find that the *Streptococcus viridans* is so constantly present in the tonsils of these patients. Vaccines were not used in any of the cases. As they all responded well to salicylates, vaccine therapy was hardly indicated.

#### *Streptococcus Viridans in Chronic Tonsillitis*

The two cases of this character present nothing of particular interest except in indicating that *Streptococcus viridans* is a common finding in chronic hypertrophic tonsillitis.

#### *Chronic Tonsillitis Associated with Infectious Endocarditis*

The tonsils in these two very typical cases of subacute infectious endocarditis showed no external signs of disease, but cultures from the crypts gave practically pure growths of *Streptococcus viridans* and both patients gave histories of recent "colds," which may have been localized *Streptococcus viridans* infections of the nasopharynx and tonsils.

The strains of *Streptococcus viridans* obtained from the tonsils in these two cases reacted on culture mediums in the same way as those recovered from the blood. Morphologically, however, the cocci from the tonsils were somewhat larger than those from the blood.

Autogenous vaccines, both the killed and the sensitized living, were administered in both these cases. At times the vaccine seemed to reduce the temperature, but the effect was only temporary.

#### *Chronic Tonsillitis Associated with Chronic Arthritis*

There were three cases of this character in which *Streptococcus viridans* predominated in cultures from the tonsil. In these three cases the existence of tonsillar disease was quite evident. In every instance smears from the tonsillar crypts showed pus cells in addition to Gram-positive diplococci. In the first case, the tonsils were removed and autogenous vaccine administered, and the patient's joints began to improve immediately. In the other two the tonsils were not removed and the condition of the patients remained unchanged, though one of them received large doses of autogenous vaccine. The first case was much less advanced than the other two, and hence was more amenable to treatment. This patient eventually made a complete recovery.

17. Poynton and Pane: Lancet, London, 1900, ii, 861; *ibid.*, 1910, i, 152, 1528.

Two of the cases in this series illustrate a condition which I have observed several times, namely, the combination of both pyorrhea and tonsillitis with arthritis.

STREPTOCOCCUS VIRIDANS IN INFECTION OF THE ALVEOLAR SOCKETS  
(PYORRHEA ALVEOLARIS; ALVEOLAR ABSCESS)

The only extensive study of the bacteriology of pyorrhea is that of Goadby,<sup>18</sup> who in ninety cases, found the streptococcus in fifty-five and the staphylococcus in sixty-three of them. His cultures were taken on slant agar. No one organism has ever been held responsible for pyorrhea, but Ankovy<sup>19</sup> thought that the disease was probably of streptococcic origin. In the more recent studies of oral sepsis and its relation to systemic disease, some form of streptococcus has usually been found present, often in association with *Bacillus fusiformis* and spirochetes. My own series comprises 15 cases.

*Technic of Taking Cultures*

Before taking the cultures the teeth were subjected to a thorough cleansing by a dentist. If this was not possible, a nurse scrubbed the teeth and gums well with potassium chlorate. When the culture was to be taken the gum was rubbed off with alcohol, dried with a sterile gauze sponge and a drop of pus squeezed out. A loopful was then transferred to blood-agar plates, and another loopful smeared on glass slides.

From all of the fifteen cases studied an abundant growth of *Streptococcus viridans* was obtained, in some cases practically pure.

Pyorrhea is exceedingly common among the lower classes and is frequent enough in all classes. Filthy teeth, the gouty diathesis, improper bridge-work, etc., are important predisposing causes. The infection is usually secondary, developing after the gum and root membrane have been subjected to chemical or mechanical injury. Autogenous vaccines have been beneficial in some cases. In one case of the present series an autogenous *Streptococcus viridans* vaccine eliminated that organism from the discharge and produced considerable diminution in its amount. Smears, however, showed the persistence of large numbers of spirochetes. Anaerobic cultures were now taken on Noguchi's ascitic agar medium and a pure growth of *Treponema microdentium* was obtained. A vaccine was prepared from this organism, and two inoculations were given. The patient then went abroad and the treatment was never resumed. Pyorrhea in most cases remains a purely local infection, but there is considerable

18. Goadby: Lancet, London, 1907, i, 632.

19. Ankovy: Quoted by Goadby, reference not given.

evidence to show that in some instances it is responsible for certain systemic disorders.

*Streptococcus Viridans in Infection of the Alveolar Sockets Associated with Acute Arthritis.*—There was only one case of this type, an acute polyarthritis of the rheumatic fever type, associated with marked pyorrhea. In the absence of any other local lesion in this case one is led to suspect that the infected tooth sockets were the foci from which the joints were infected. It is unfortunate that in this case no cultures were taken from the joints. Cultures taken according to Rosenow's technic might have given positive results.

*Streptococcus Viridans in Infection of the Alveolar Sockets Associated with Chronic Arthritis.*—There were four cases of this character in which *Streptococcus viridans* was the predominant organism in the cultures from the tonsillar crypts. These cases are of a type that is being recognized more and more frequently. Just how responsible pyorrhea is for the joint changes in chronic arthritis it is at present impossible to say. Rosenow<sup>20</sup> has recently been able to cultivate a streptococcus closely resembling the *viridans* from lymph-glands adjacent to such joints, a fact which would suggest a rather close connection. Certainly many of these cases improve when the condition in the mouth is corrected. This is particularly true in the earlier cases, in which bony changes have not yet occurred. In two out of the four cases just reported there was improvement after the pyorrhea had received attention and autogenous vaccines had been given. One case has not been heard from. This case, by the way, afforded another instance of the association of tonsillitis with pyorrhea.

*Streptococcus Viridans in Infection of the Alveolar Sockets Associated with Chronic Nephritis.*—The occasional association of nephritis with tonsillitis has long been recognized, but little attention has been paid to pyorrhea as an etiological factor in disease of the kidney. I have studied the bacteriology in two cases of pyorrhea associated with chronic nephritis. In both of them *Streptococcus viridans* was the predominant organism. One of the cases was particularly interesting in that the patient had a high temperature and showed many petechiae on the body. Under the usual treatment, which was augmented with dental hygiene and an autogenous vaccine, the temperature returned to normal and the patient made considerable improvement.

*Streptococcus Viridans in Infection of the Alveolar Socket Associated with Chronic Infectious Endocarditis.*—This was a typical case of infectious endocarditis and needs no comment further than to say

20. Rosenow, E. C.: Etiology of Arthritis Deformans, Jour. Am. Med. Assn., 1914, lxii, 1146.



that if the alveolar abscess had been discovered in time, the patient would probably never have developed endocarditis. The streptococcus obtained from the abscess was practically identical with that found in the blood, the only difference being that the former was a little larger in size.

#### STREPTOCOCCUS VIRIDANS IN INFECTION OF THE PHARYNX AND THE NASAL CAVITIES

The bacteriology of coryza has been extensively studied, but in spite of this there still remains considerable disagreement and doubt on the subject. Cultures from coryzas in the acute stage are often sterile, while in cultures taken in the subacute or chronic stage, there are often several types present, so that it is difficult to decide which organism is the causative factor.

Various bacteria have been considered as more or less specific for colds. Cautley<sup>21</sup> in 1894 described a small bacillus, since known as *Bacillus septus*, which he considered the exciting agent in the majority of colds. White<sup>22</sup> and Walter<sup>23</sup> have also attributed considerable importance to *Bacillus septus* in the etiology of colds. Recently, Tunnicliff<sup>24</sup> has described a small spirochete which she has been able to isolate from acute and chronic coryzas. Allen<sup>25</sup> makes the statement that the streptococcus is the most frequent cause of "purulent nasal catarrh," referring doubtless to subacute and chronic coryzas. Numerous writers have shown that the normal nasal cavity is sterile or practically so. Hasslauer<sup>26</sup> studied seventy-eight cases of nasal catarrh and found that in acute cases streptococcus, pneumococcus and the pseudodiphtheria bacillus were most numerous and most frequently found. Schottmueller,<sup>6</sup> in his original study of *Streptococcus viridans*, frequently found this organism almost pure in acute and chronic rhinitis.

The *Streptococcus viridans*, like the pneumococcus, is an inhabitant of the normal mouth. It is usually easy to isolate it on plates from any healthy pharynx.

#### *Acute Coryza with Pharyngitis*

I have studied only a limited number of coryzas, eight in all. In taking cultures from the nose, the vestibules were first cleaned out with soap and water, and then a plug of absorbent cotton soaked with

21. Cautley: Ann. Rep. Local Govt. Bd. Med. Suppl., 1894-1895, xxiv, 455.

22. White: Catarrhal Fevers, London, 1906, p. 54.

23. Walter: A Study of the Bacterial Flora of the Nasal Mucosa in the Presence of Rhinitis, Jour. Am. Med. Assn., 1910, lv, 1091.

24. Tunnicliff: Jour. Infect. Dis., 1913, xiii, 283.

25. Allen: Brit. Med. Jour., 1906, ii, 721; Lancet, London, 1908, ii, 1589, 1659.

26. Hasslauer: Centralbl. f. Bakteriöl., 1902, xxxiii, 47.

95 per cent. alcohol was inserted in each nostril and allowed to remain there several minutes. When the plugs had been removed a sterile nasal speculum was inserted and several loops of secretion from the middle meatus were carefully removed with a platinum wire and smeared over the plates. In some cases the patient was asked to blow on a piece of sterile gauze. Some of the secretion was then washed with sterile saline and plated in the usual manner.

Cultures from the pharynx were taken with a sterile swab, after the throat had been well gargled with sterile salt solution.

Of the eight cases so studied, five gave evidence of being of *Streptococcus viridans* origin.

*Streptococcus viridans* coryzas frequently start in the throat and extend upward or downward, or both. They show a distinct tendency to recur. This was very noticeable in two of the cases. In view of the close relation of *Streptococcus viridans* to the pneumococcus, it is noteworthy that in two cases the patients had previously suffered from pneumococcus infections. In one case autogenous *Streptococcus viridans* vaccine was given a thorough trial and proved most effective in protecting the patient against subsequent infection. The inoculations were started in January and were repeated once a week through the remainder of the winter and early spring.

#### STREPTOCOCCUS VIRIDANS IN INFECTION OF THE ACCESSORY SINUSES

It has been shown by Toerne<sup>27</sup> that healthy sinuses are practically always free from bacteria. Herzfeld and Hermann<sup>28</sup> studied the bacteria in ten cases of antral empyema and found non-virulent streptococci (probably *viridans*) in eight of them. In six cases the streptococcus either was present in pure culture or was noted as the predominant species. Howard and Ingersoll,<sup>29</sup> in eighteen cases of sinus infection, obtained the streptococcus in half of them (four times in pure culture) and the pneumococcus in four. Lichtwitz,<sup>30</sup> in a study of sinus infections, concludes that the streptococcus and staphylococcus are responsible for most sinus infections. Stanculeanu and Baup<sup>31</sup> divide facial empyema into two groups: first, the fetid type, in which infection takes place through the teeth; anaerobes are usually most active in these; and second, non-fetid types, infection through the nose, usually due to streptococcus or pneumococcus. Lewis and Turner's<sup>32</sup>

27. Toerne: Centralbl. f. Bakteriöl., 1903, xxxiii, 250.

28. Herzfeld and Hermann: Arch. f. Laryng. u. Rhinol., 1895, iii, 143.

29. Howard and Ingersoll: Am. Jour. Med. Sc., 1898, cxv, 520.

30. Lichtwitz: Prag. med. Wchnschr., 1894, 31.

31. Stanculeanu and Baup: Arch. de Sc. méd., 1900, v, 121.

32. Lewis and Turner: Edinburgh Med. Jour., 1905, ii, 393.

study of the bacteriology of sinus infection covers seventy-four cases. In the acute cases, streptococci were present in 60 per cent.; in the chronic cases in 80 per cent. The pneumococcus was found in almost as large a percentage. Allen's<sup>33</sup> results in thirty cases of sinusitis differ from previous studies in showing a high incidence of *Bacillus influenzae* (73 per cent.). The streptococcus or pneumococcus or both, were present, however, in 80 per cent. of the cases also.

I have studied the flora in eight cases of sinus infection. The cultures were obtained under strict bacteriological technic. In all but one of the cases I was assisted by a laryngologist who aspirated the pus from the sinus with sterile instruments.

In three cases I found the *Streptococcus viridans* predominant. One was an antrum infection, another frontal, and in the third, both were involved. In the last, the patient suffered from severe attacks of bronchial asthma.

It is often difficult to cultivate the *Streptococcus viridans* from the sinuses, even when the organisms can be seen in smears. This was my experience in two cases, in which repeated cultures were sterile. This is particularly liable to occur if the pus has been allowed to remain for several days in the sinus. Freshly secreted pus is much more likely to give a growth than old pus in which presumably the bacteria have been destroyed by bactericidal substances.

Chronic sinus infections of whatever origin do not yield readily to vaccine treatment or to any other form of treatment. One of my patients was considerably relieved from frontal headache by large doses of autogenous *Streptococcus viridans* vaccine. The discharge was diminished, but did not entirely disappear.

In one case of sinusitis associated with asthma there was considerable sensitiveness to *Streptococcus viridans* vaccine. An injection of 100 million produced within five hours a very marked general reaction which lasted twenty-four hours. There were general malaise, fever and increased secretion from the sinuses. Fortunately, this sensitiveness has now disappeared, so that he is able to take doses of 2 billion or more without trouble. The asthma has improved, but the sinuses remain about the same.

#### STREPTOCOCCUS VIRIDANS IN INFECTION OF TEAR SAC (CHRONIC DACRYOCYSTITIS)

I have studied the bacteriology of only one case of dacryocystitis, and this proved to be a pure infection of *Streptococcus viridans*. Removal of the sac resulted in complete cure.

33. Allen: Bacterial Diseases of Respiration, Philadelphia, 1913, p. 53.

## STREPTOCOCCUS VIRIDANS IN INFECTION OF THE MIDDLE EAR

*Streptococcus viridans* infections of the middle ear are unusual. *Streptococcus haemolyticus* or *mucosus*, or the pneumococcus are more frequently found in the acute cases, and *Staphylococcus aureus* or *albus* in the chronic. Out of seven cases studied, I have encountered only one of *Streptococcus viridans* otitis. This was in a boy 5 years old. The infection ran a short, mild course, and the mastoid was not involved.

## STREPTOCOCCUS VIRIDANS IN INFECTION OF THE TRACHEA AND BRONCHI

The bacteriology of bronchitis has been studied thoroughly by many observers, but most of these studies were made before blood-agar mediums came into general use. I have not investigated the literature earlier than 1900, but since that time there have been a number of careful studies of the subject. Marfan<sup>34</sup> found that the streptococcus and pneumococcus were the organisms most frequently found in bronchitis. Forscheimer<sup>35</sup> noted that the streptococcus always replaced the influenza bacillus in influenza bronchitis. Babes and Beldiman,<sup>36</sup> and Bartel<sup>37</sup> have emphasized the importance of streptococcus and pneumococcus in bronchitis. Pollak<sup>38</sup> in 1908 studied 73 cases of purulent bronchitis at necropsy and found the pneumococcus 41 times; the streptococcus 27 times, and the *Staphylococcus aureus* 31 times. Other bacteria were much less frequent.

Ritchie<sup>39</sup> examined the bacteria in 49 cases of bronchitis with the following results: Streptococcus was present in 34 cases (70 per cent.), pneumococcus in 46.9 per cent. He concludes that "these two are certainly the most important causal bacteria in bronchitis." Hastings and Niles<sup>40</sup> have recently studied the bacteriology of bronchitis and pneumonia and have found streptococcus, pneumococcus and *Micrococcus catarrhalis* the most frequent invaders. Holt's<sup>41</sup> results in 354 cultures from bronchitis in children are interesting. The pneumococcus

34. Marfan: *Traité de médecine*, 1901, vi, 281.

35. Forscheimer: *Med. News*, 1901, lxxviii, 851.

36. Babes and Beldiman: *Ann. de l'Inst. de path. et de bact. de Bucarest*, 1894, 145.

37. Bartel: *Centralbl. f. Bakteriöl.*, 1898, xxiv, Part 1, p. 401.

38. Pollak: *Wien. klin. Wchnschr.*, 1908, xxi, 973.

39. Ritchie: *Jour. Path. and Bacteriol.*, 1901, vii, 1.

40. Hastings and Niles: *Jour. Exper. Med.*, 1911, xiii, 638.

41. Holt, L. E.: *The Bacteriology of Acute Infections of the Respiratory Tract in Children*, with Especial reference to Influenza, *THE ARCHIVES INT. MED.*, 1910, v, 449; *The Bacteriology of Acute Respiratory Infections in Children as Determined by Cultures from the Bronchial Secretion*, *Jour. Am. Med. Assn.*, 1910, lv, 1241.

was present in 231 cases, the streptococcus in 109, and the *Staphylococcus aureus* in 266. In none of these studies has the distinction between the *Streptococcus viridans* and *Streptococcus haemolyticus* been brought out.

During the past two years I have studied the sputum from fourteen cases of bronchitis (acute and chronic). In eight of these the *Streptococcus viridans* was predominant or present in pure culture. Kitasato's method was used in making the examinations. Freshly expectorated sputum was washed several times with salt solution, then a small portion was removed from the center of one of the masses and smeared over blood-agar plates.

*Acute Bronchitis.*—Acute bronchitis of *Streptococcus viridans* origin is usually mild, as all other infections with this organism tend to be. Three out of the four cases studied were subject to repeated acute attacks, again illustrating the failure of the body to develop a permanent immunity against this organism. Only one of these patients was vaccinated against *Streptococcus viridans*. Case 4 received autogenous vaccine every five to seven days through the late winter and spring, and has had no more infections of any kind since the vaccine treatment has been instituted.

*Chronic Bronchitis.*—Four of the six chronic bronchitis cases showed a predominance of *Streptococcus viridans* in the sputum. When I compared these four cases I was surprised to find that they all had with their cough more or less well-defined asthma. This is probably a coincidence, but agrees with the work of Allen, who found streptococci in the sputum of practically all asthmatics. In the first two cases the asthmatic symptoms were quite typical. The second case had in addition a quiescent tuberculous process. According to Allen, there are some cases of asthma in which vaccine is of benefit. It was employed in only one of this series. Autogenous vaccine was given through the entire winter and by this means the cough was kept well in control. When the vaccine was omitted for any length of time, however, the symptoms recurred.

#### CLINICAL COURSE

If one studies the general clinical course of *Streptococcus viridans* infection of the upper respiratory tract, they are seen to have three very definite characteristics:

1. They usually run a mild course. The *Streptococcus viridans* is essentially a germ of low virulence for animals and man alike. In the present series of cases the severe infections have nearly always been caused by the pneumococcus or the *Streptococcus haemolyticus*.

2. They have a tendency to become chronic. This applies particularly to pyorrhea, tonsillitis and sinusitis. *Streptococcus viridans* bronchitis and rhinitis often run a chronic course also.

3. They are followed by little or no immunity and are therefore quite prone to recur at frequent intervals. This trait, well illustrated in the coryza and bronchitis series, follows from the low virulence which the organism possesses. Its metabolism disturbs the body so little that only a small amount of protective substance is developed against it.

The present study gives some weight to the idea that *Streptococcus viridans* infections play an important part in the etiology of certain systemic diseases, especially arthritis, endocarditis and nephritis. *Streptococcus viridans* can usually be isolated from the crypts of the tonsil in acute rheumatism. Rosenow has cultivated streptococci from the joints in acute rheumatism, and has found that except for slight variations they differ in no way from *Streptococcus viridans*. Davis found *Streptococcus haemolyticus* more commonly in the tonsils of chronic arthritis and nephritis, but, in my own experience, the *viridans* is just as frequently found in these diseases.

It is noteworthy that of all the *Streptococcus viridans* infections of the upper respiratory tract, it is almost exclusively those of the tonsils and tooth sockets (occasionally of the sinuses) that are associated with systemic disease. Rosenow's studies on the transmutation of streptococci and pneumococci are interesting in this connection. To quote Rosenow:

The fact that variations in oxygen tensions and salt concentration, that growth in symbiosis with other bacteria and that injections into cavities in animals commonly call forth mutational forms in streptococci suggests strongly that similar changes might occur in various foci of infection where such conditions may prevail. It would seem therefore that focal infections are no longer to be looked upon merely as a place of entrance of bacteria but as a place where conditions are favorable for them to acquire the properties which give them a wide range of affinities for various structures.

The places in the human body where such conditions prevail are apparently the tonsils, sinuses and tooth sockets. By this reasoning can be explained the slight differences which have been noted between the strain of streptococcus isolated from the mouth and that obtained from the heart valve or joint.

#### VALUE OF VACCINES

There remains to be considered the value of vaccines in the treatment and prevention of *Streptococcus viridans* infections. As a result of the present study I feel no hesitancy in saying that autogenous vaccine may be of great value in selected cases of subacute and chronic



infection by this organism. Naturally, in those cases in which the infection is accompanied by extensive structural changes, as, for example, bronchitis with emphysema or bronchiectasis, old sinus infections with thickened walls, advanced pyorrhea with retraction of the gums, and tonsillitis with hypertrophy, the benefit which a vaccine can bestow is limited.

It is in the prevention of recurrences of these infections that vaccine is most valuable. In several cases of my series, patients who had been subject to frequent reinfections were successfully carried by means of vaccination through the winter and spring without any further recurrence of these troubles.

Prophylactic vaccination against infections of the upper respiratory tract is a matter which deserves more study. It is rather strange that prophylactic vaccination of dogs against distemper should be so generally in use, while so little effort is being made to protect human beings against coughs and colds. From my own experience, I should favor the view that most persons who suffer from frequent colds are susceptible to one particular organism with which they are constantly being reinfected. Moreover, the more carefully one studies these cases, the less weight he attaches to the idea of their being usually mixed infections. It is probably one organism that causes the infection in most cases. The others, being present on the infected surface, multiply in the rich secretions which are poured out, and simply serve to confuse the bacteriological picture. If this is the case there is all the more reason why every effort should be made to discover the offending organism, and if necessary to protect the patient against further infection.

#### SUMMARY

1. In a bacteriological study of eighty-nine infections of the upper respiratory tract, the *Streptococcus viridans* has been the predominant organism in fifty cases, or 56.2 per cent. If the cases in which the pneumococcus or *Streptococcus haemolyticus* were predominant be added to this group, it can be said that in 85 per cent. of the cases studied, one or the other of these closely allied species was apparently concerned in the infection.

2. *Streptococcus viridans* infections of the upper respiratory tract are characterized by their mild course and a tendency to chronicity and frequent recurrences, owing in great measure to the short duration of the acquired immunity.

3. *Streptococcus viridans* infections of the upper respiratory tract, especially those of the tonsils, sinuses and alveolar sockets, are frequently associated with endocarditis and arthritis. In these cases there

is much evidence in favor of the theory that the infections of the serous membranes are secondary to the infections of the upper air passages.

4. Autogenous *Streptococcus viridans* vaccines are of considerable value in cases in which structural changes are not too advanced. Their administration may also be useful in the prevention of recurrences.

123 East Sixty-second Street.

## A CASE OF INDEPENDENT VENTRICULAR ACTIVITY OCCURRING DURING ACUTE ARTICULAR RHEUMATISM \*

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NEW YORK

*History.*—S. P., male, aged 20, entered the Har Moriah Hospital, Feb. 4, 1913. He had measles when 3 years old and typhoid when 10; otherwise there was no history of any previous illness. He was not addicted to tea, coffee, tobacco or alcohol. Five days before admission he developed a typical attack of acute articular rheumatism involving the ankles, wrists, knees and elbows. The attack was accompanied by fever; there were no chills or gastric disturbances.

On admission, except for swelling and redness of the inflamed joints, the physical and neurological examination revealed nothing abnormal. There was no urethral discharge. The complement-fixation test for gonococci was negative. The cardiac outline was normal to percussion, the apex beat was in the fifth interspace, 8.5 cm. from the midsternal line; the heart sounds were normal; the pulse was rhythmical. The systolic and diastolic blood-pressure were within normal limits. The temperature ranged between 101 and 103. There was no dyspnea. The patient did not appear very ill; sodium salicylate in moderate doses was given for two days.

Two days after admission a transient pulse irregularity appeared. Six days thereafter, it recurred once in about fifteen beats and clinically resembled extrasystoles; no tracings were made at that time. February 12, the irregularity occurred every third or fourth beat. From that day frequent polygraphic and later electrocardiographic tracings were taken. February 14, for the first time a rough blowing systolic murmur was heard at the apex. Occasionally there were runs of from three to twelve stronger thumping beats accompanied by the murmur; studies of the tracings showed that these beats were due to simultaneous action of auricle and ventricle. Four days later the arrhythmia was very infrequent, the systolic murmur had almost entirely disappeared. The patient left the hospital feeling well.

*Polygraphic and Electrocardiographic Tracings.*—In Figure 1, *a*, *b*, *c* are continuous parts of polygraphic tracings taken February 12. In Figure 1 *a*, with the exception of three rhythmic beats (5, 6, 7 in the venous curve of Figure 1 *a*) independent ventricular action is present, as is evidenced by the carotid wave, *c*, falling with or preceding the auricular wave, *a*; one ventricular extrasystole (*v'*) is also present. Figure 1 *b* shows a similar arrhythmia with varying *c-a* intervals and occasional simultaneous action of auricle and ventricle. The rhythm again becomes normal in the last section of the tracing (Fig. 1 *c* at *n*). The average pulse-rate throughout is sixty per minute, though the beats which inaugurate the normal rhythm (Figure 1 *c*, *X'* and *X''*) are somewhat more rapid. The entire tracing is typical of those taken on the days when the arrhythmia was marked (for instance, Fig. 2, *a* and *b*). One week later the pulse was rhythmical except for an occasional independent ventricular contraction (Fig. 3 at *f*), the rate about 57 per minute. February 26, the rhythm was normal, the rate 70. Subsequently, pressure on the vagi was practiced to study its effect on the rhythm. Left vagus pressure showed a transient increase of pulse rapidity (Fig. 4). During right vagus pressure (Fig. 5) there was slight temporary slowing of the pulse-rate. Neither right nor left vagus pressure had any effect on the normal auriculoventricular sequence. After sufficient time

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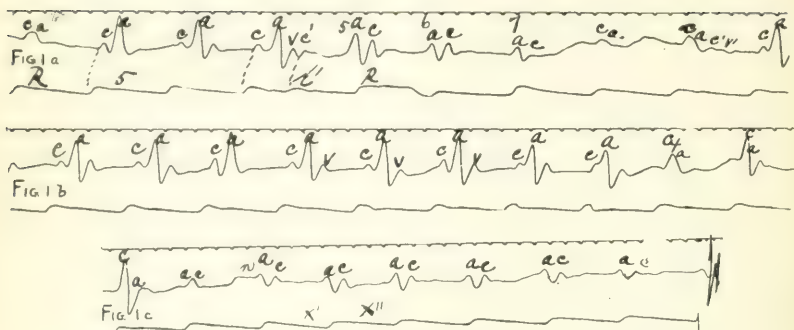


Fig. 1.—Continuous polygraphic tracing taken February 12. In Figure 1 *a*, except beats 5, 6 and 7 (venous tracing), independent ventricular beats are present; the carotid wave, *c*, precedes or falls with the auricular wave, *a*. *R* = radial pulse; *r'* = ventricular extrasystole. Average pulse-rate is 60 per minute. In Figure 1 *b*, ventricular automatism with varying *c-a* intervals and occasional simultaneous action of auricle and ventricle (superposition of *a* and *c*) are present. Figure 1 *c*, rhythm becomes normal at *n*. *X'* and *X''* and somewhat more rapid beats which inaugurate the normal rhythm.

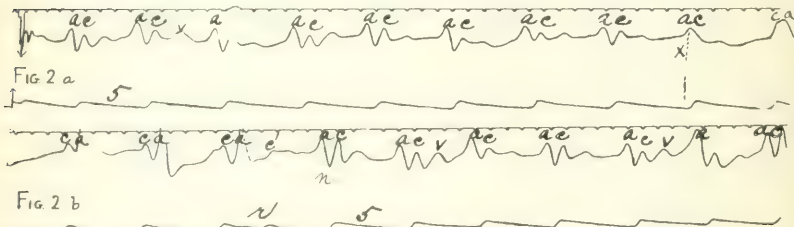


Fig. 2.—Continuous tracing taken February 13. The automatic beats begin at *X*. The rhythm is again normal at *n* (Fig. 2 *b*). The numerals on the radial beats represent their lengths in fifths of a second. Except for extrasystole (*r'*) the rhythm has been normal, the rate 60 per minute.

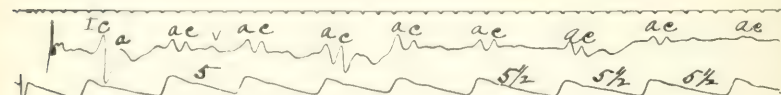


Fig. 3.—Section of a long polygraphic tracing taken February 19. It shows one independent ventricular contraction at *I*.

had been allowed for the heart to recover from vagus pressure, atropin sulphate, 1/30 grain, was injected subcutaneously and a continuous polygraphic tracing lasting one hour was taken, the important sections of which are reproduced (Fig. 6, *a* and *b*). They show that ten minutes after the injection ventricular automatism was occasionally present; the rate throughout was 60 per minute. Immediately preceding this arrhythmia, the rhythm had been normal with an occasional increase of rate to 75 per minute. At the end of the atropin experiment the pulse-rate was 100, the beats sequential.

Many electrocardiograms were taken, two of which are given (Figs. 7 and 8). The rhythm is normal in the first lead (Figure 7, *a*). In the first section of

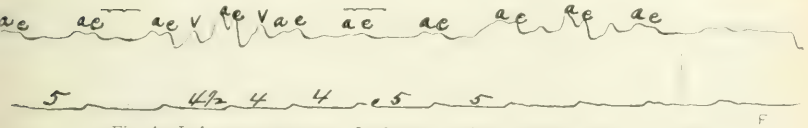


Fig. 4.—Left vagus pressure. It shows transient increase of the pulse-rate. The venous curve is somewhat distorted by the digital pressure on the vein.



Fig. 5.—Right vagus pressure. It shows slight transient slowing of the pulse-rate; later the rate increased.

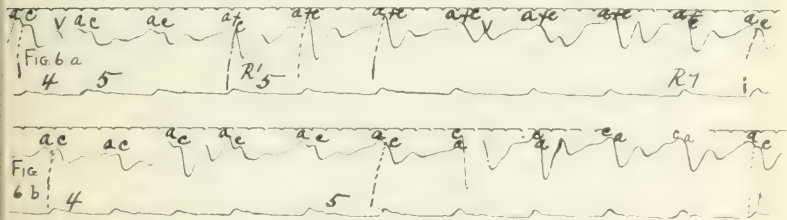


Fig. 6 *a*.—Ten minutes after subcutaneous injection of atropin sulphate, 1/30 grain. The incidence of *c* in the jugular tracing is shown by the dotted lines. Ventricular automatism is present from  $R^1$  to  $R^7$ . The ventricular rate is 60 per minute. Fig. 6 *b*.—Fifteen minutes after atropin injection. It shows several automatic beats; the ventricular rate is 60 per minute.

the second lead (Figure 7, *c*), there is a slight difference in the length of the diastolic pauses, an arrhythmia apparently of sinus origin. There are several automatic beats (Fig. 7, *c*,  $R^2$ ,  $R^3$ ,  $R^4$ ) in the second part of the same lead. The beats are again sequential in the third lead (Fig. 7, *d*). Three days later, February 25, an electrocardiogram, second lead only (Fig. 8, *a* and *b*), was taken, ten and fifteen minutes, respectively, after the subcutaneous injection of 1/30 grain of atropin sulphate. With the exception of slight sinus arrhythmia,

the beats are rhythmical, the ventricular rate about 60 per minute. Twenty minutes after the injection, independent ventricular activity with approximately the same ventricular rate is present (Fig. 8, *c*). In the later tracings (Fig. 8, *d*, *e*) normal auriculoventricular sequence is reestablished. It is important to note that the idioventricular and sequential complexes are identical throughout. Subsequent electrocardiographic tracings, the last taken three months after the onset of the arrhythmia, show that the latter has not recurred.

## COMMENT

Abnormal cardiac mechanisms similar to this have been ascribed to various causes. When auricles and ventricles beat at such rates that

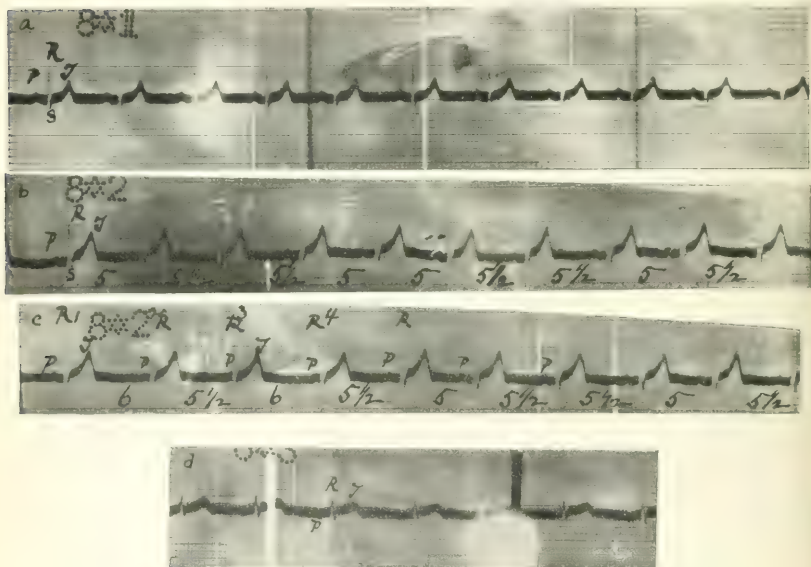


Fig. 7.—Electrocardiogram taken February 22. P = auricular deflection, R, S, T = ventricular complex. Fig. 7, *a*.—Lead 1 shows normal rhythm. Fig. 7, *b* and *c*.—Continuous parts of Lead 2. The numbers beneath the complexes represent the lengths of the beats in fifths of a second. Fig. 7, *b* shows slight sinus arrhythmia. Fig. 7, *c*.— $R^2$ ,  $R^3$  and  $R^4$  are automatic ventricular contractions as shown by the varying P-R intervals. Slight sinus arrhythmia is also present. Fig. 7, *d* (Lead 3).—The rhythm is again normal.

their waves and deflections in the tracings are regularly superimposed, their origin in or near the auriculoventricular node has sometimes been assumed; these are called nodal extrasystoles.<sup>1</sup> Such simultaneous

1. Lewis: *Quart. Jour. Med.*, 1912-1913, vi, 221. Laslett: *Ibid.*, vi, 210. Cowan, Fleming and Kennedy: *Lancet*, London, 1912, i, 207.



action is seen in parts of the tracings (Fig. 1, *a* and *b*; Fig. 8, *c*), but it apparently depends on *transient* identical auricular and ventricular speeds, for as the latter vary, varying *a-c* and *c-a*, or P-R intervals soon occur. Besides, nodal beats are usually either regularly interpolated in the normal rhythm, or when premature, are followed after longer or shorter compensatory pauses by the normal dominant beat.

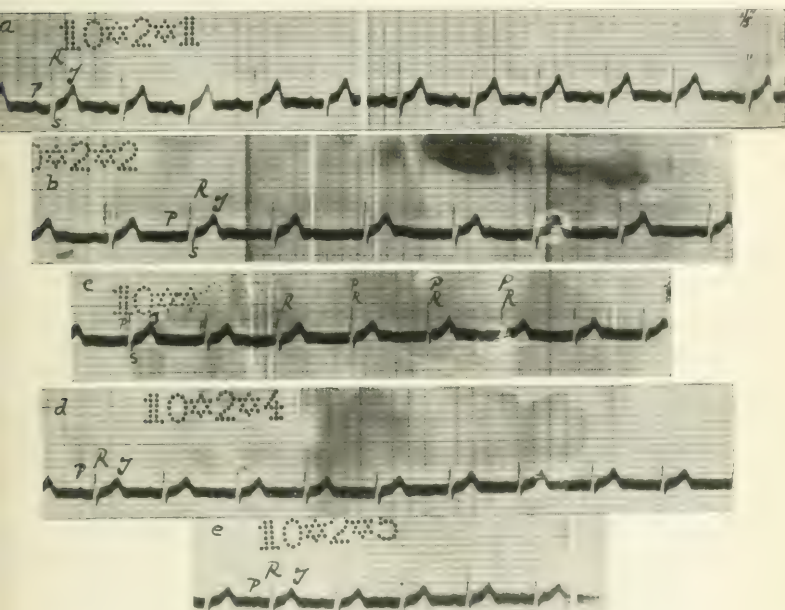


Fig. 8.—Taken February 25. Lead 2; sections taken after the subcutaneous injection of atropin sulphate, 1/30 grain. The time marker measures one-fifth second. Figure 8, *a* and *b*.—Ten and fifteen minutes, respectively, after atropin injection. Slight sinus arrhythmia is present; the ventricular rate is about 60 per minute; the auriculoventricular sequence is normal. Fig. 8, *c*.—Twenty minutes after the injection. It shows ventricular automatism, with decreasing P-R intervals and finally simultaneous action of auricle and ventricle (superposition of P and R). Fig. 8, *d* and *e*.—Twenty-five and thirty-five minutes, respectively, after atropin. The beats are again sequential.

assumptions apparently not warranted by the electrocardiograms, all of whose complexes are alike. Retrograde conduction from ventricle to auricle, a rare reversal of the cardiac mechanism,<sup>2</sup> requires consider-

ation as a possible explanation. In the clinical case<sup>3</sup> described, the rhythm when established showed a definite ventriculo-auricular conduction time similar to the normal, and was accompanied by marked ventricular slowing. This conception if applied to my case would necessarily also assume that the reversed mechanism suddenly and irregularly ceased from time to time in such sections of the tracings which do not show a retrograde conduction time (*c-a* or R-P intervals) of less than one-fifth second, and that frequently occasional isolated beats were retrograde — assumptions which seem highly improbable and are not warranted by the tracings. Rihl<sup>4</sup> describes a case of occasional automatic ventricular action produced by vagal pressure. Lewis<sup>5</sup> reports a case of rheumatic mitral stenosis with decompensation; digitalis had been given with consequent ventricular automaticity ("ventricular escape," Lewis). Gallavardin, Dufourt and Petzetakis<sup>6</sup> describe three cases with slow pulses (in one case the rate was 36 per minute) in which there was no clinical evidence of organic cardiovascular disease. Numerous polygraphic and electrocardiographic tracings show the spontaneous occurrence of ventricular automatism in two cases; in all three it was readily evoked by ocular and vagus pressure and by atropin injection. They suggest two main causes for the phenomena: relative retardation of the auricular as compared with the idioventricular rate, or acceleration of the latter beyond the former. Two of their cases had very slow auricular rates occurring either spontaneously or induced by the methods described; the third showed no auricular retardation on vagus or ocular pressure, or after atropin injection. The arrhythmia in the first two cases was apparently due to relatively increased idioventricular rapidity beyond that of the sinus. Except for a very slight change in the complexes of the automatic ventricular beats in two of the cases — the absence of a very small S wave — all of the complexes are identical. In digitalis poisoning, Cohn and Fraser<sup>7</sup> have occasionally found either identical auricular and ventricular speeds or ventricles beating more rapidly than auricles with ventricular escape. In my case there is at no time any marked pulse retardation — the lowest rate is 55 — nor is there any evidence of definite auricular slowing, though there is at the periods of ventricular automatism some difference, always slight, between auricular and ventricular rapidity. Except for occasional somewhat slower beats,

2. Cohn, Kessel and Mason: *Heart*, 1911-1912, iii, 321.

3. Williams and James: *Heart*, 1913-1914, v, 109.

4. Rihl: *Deutsch. Arch. f. klin. Med.*, 1904, xciv, 286.

5. Lewis: *Quart. Jour. Med.*, 1908-1909, ii, 356.

6. Gallavardin, Dufourt and Petzetakis: *Arch. d. mal. du cœur*, 1914, i, 1.

7. Cohn and Fraser: *Internat. Med. Cong.*, 1913, Section 6, Part 2, p. 258.

the idioventricular and normal ventricular rates are approximately the same. Slight sinus arrhythmia is sometimes present, but is not more marked than is frequently found as a physiological phenomenon.

As possible causes for the production of automatic ventricular action, neurogenic, toxic and organic factors require consideration. A neurogenic factor in the sense of a so-called neurosis due to extracardial conditions (for example, gastric disorders) causing abnormal peripheral disturbances in the centripetal arm of a reflex arc can be here dismissed because of the type of the disease, its course and the definite completion of the arrhythmia with the end of the rheumatic attack. Though the action of toxins is an extremely complicated one and to a great extent at present unknown, it seems to depend on their complicated chemical composition and on intricate chemical reactions taking place in the body. It has been pointed out that digitalis poisoning may produce ventricular escape. By analogy, it seems theoretically possible that a rheumatic toxin may also produce a similar arrhythmia, though there is no clinical proof for the assumption. Regarding an organic cause for the arrhythmia, it is recalled that the patient developed a loud systolic murmur at the apex, one week after the appearance of the arrhythmia; the murmur remained for two days, then gradually disappeared. It also disappeared when auricle and ventricle contracted simultaneously, an apparent corroboration that it was due to mitral insufficiency, organic or relative in nature. It is not my intention to discuss cardiac murmurs at any length, the etiology of many of which is not definitely known. Systolic apical murmurs which occur during the course of any febrile disease and then disappear without evidence of an organic cardiac lesion are by no means infrequent. On the other hand, organic murmurs usually increase in intensity and do not disappear. The occurrence of the murmur in conjunction with acute articular rheumatism makes its presence suspicious of some slight, possibly transient, valvular or myocardial involvement. Rheumatic infections cause myocardial inflammation in the form of submiliary myocardial nodules (Aschoff bodies). Healed or healing isolated Aschoff bodies have been found on the interventricular septum in hearts which were the subjects of rheumatic reinfection;<sup>8</sup> during their inflammatory state, if situated close to or even partly involving the bundle of His, before its division, they may conceivably cause sufficient local irritation to produce occasional ventricular automatism with beats of supraventricular origin, and yet the bundle need not be sufficiently compromised to prevent the idioventricular impulse from following its normal course in the conduction system—a fact which probably

8. Thalheimer and Rothschild: *Jour. Exper. Med.*, 1914, xix, 417.

accounts for identical electrocardiographic complexes of all beats, rhythmic and arrhythmic.

Right and left vagus pressure had no effect on auriculoventricular sequence. One of the atropin experiments was followed by a number of independent ventricular contractions, with no marked difference between ventricular and auricular rates. This observation does not necessarily exclude the possibility of an organic cause for ventricular automatism because an irritative lesion which does not entirely and permanently compromise the bundle may upset the normal nerve control and mechanism and make it susceptible to atropin poisoning. It would thus seem that the automatic ventricular mechanism was not sufficiently sensitive to respond to vagus pressure, but that atropin poisoning prevented the inhibitory vagus control and permitted ventricular escape.

#### SUMMARY AND CONCLUSIONS

A case of independent ventricular activity is described. The lowest ventricular rate is 56 per minute, the usual rate is 60 and remains so whether ventricular automatism is present or not. The electrocardiographic complexes of all beats are identical. At one time atropin injection is followed by ventricular escape. The occurrence of the automatic activity during the course of acute articular rheumatism and its disappearance later and a study of the physical signs make it possible that a small transient myocardial inflammatory focus at or near the auriculoventricular connections is the irritative cause of the abnormal mechanism.

Transient independent ventricular activity may occur with no change in the path followed by the idioventricular impulse, with no difference of rate between normal and abnormal beats, and with no marked retardation of the auricular rate.

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## BOOK REVIEWS

**DISEASE AND ITS CAUSES.** By W. T. Councilman, Harvard University. New York: Henry Holt & Co.

The preface of this volume states that the author has endeavored to portray diseases as life under unusual conditions. The chapters on inflammation, cell growth, and the origin of tumors state clearly what is known on these subjects without going into unnecessary theories. The causes of infectious diseases are considered historically. Many illustrations are given of the discovery of pathogenic organisms by means of careful observation, experimentation and reasoning. The increase of disease in modern industrial life is emphasized as a check on the elimination of disease by the agencies of preventive medicine.

The book, though written for the general reader, may be read with great profit and enjoyment by the physician, for it is a philosophical as well as a scientific treatise on the most fascinating branch of medicine.

**BLOOD-PRESSURE: ITS CLINICAL APPLICATIONS.** By George William Norris, A.B., M.D. Lea & Febiger, Philadelphia and New York, 1914.

Dr. Norris's book on blood-pressure is certainly the best work on that subject in English up to date. The chapter on physiology of blood-pressure, contributed by Dr. J. Harold Austin, is an admirable summary of knowledge on that point. The account of the different instruments for measuring blood-pressure is full and clear. In fact, this account seems rather unnecessarily full; doubtless Dr. Norris felt that he would be accused of partizanship if he did not describe and picture almost all the instruments now in the market. But it appears that the time has come when such an accusation must be risked, and it is to be hoped that future books on this subject will not describe more than two or three instruments, including the ones the author finds most valuable.

The chapters on clinical aspects of blood-pressure measurement are admirable, although on page 182 the arrangement and labeling of matter is not altogether satisfactory. Possibly, too, somewhat less space might be given to the blood pressure findings in diseases in which they are really of no value. Doubtless, however, this sort of tabulation is more important in the present stage of our knowledge than it will be later on. Especially judicial and satisfactory is the account of functional tests, including both blood-pressure measurements and other methods in the study of functional efficiency of the circulation in Chapter V.

**THE MENTAL HEALTH OF THE SCHOOL CHILD.** By J. E. Wallace Wallin, Ph.D. Price \$2. New Haven: Yale University Press, 1914.

This book consists of a series of lectures and papers which have been given by the author at various times and in various places. The subject is taken up very thoroughly and contains not only a scientific consideration, but also much data in regard to the state of psycho-educational movement in this country, especially as it affects the universities and medical schools.

It distinguishes also the position in education which is taken by psychological clinics. It lays emphasis on the fact that one must be specially trained and specially endowed temperamentally to take up this intricate study with any hope of success. One is struck with the sane ideas expressed in regard to the relative position of eugenics and the scientific consideration of the welfare of the race. The author has gone extensively into the subject of the effects of physical handicaps on the mental condition.

The book ends with a chapter on a scheme for clinical study of mentally and educationally unusual children. Taken as a whole this book is an excellent treatise on the subject and worth while, not only to one who is deeply interested in the mental health of the school child, but also to one who wishes to get an unbiased opinion of the present state of scientific attainments in this line.

PROBLEMS OF GENETICS. By William Bateson, M.A., F.R.S. With illustrations. Price \$4; postage twenty-two cents. New Haven: Yale University Press, 1913.

Physicians are traditionally familiar with the study of nature. The present work shows how difficult it is for the medical man to keep up with the broad and rapid current of biologic investigation, yet it impresses on the reader the fact that more than ever, with problems of genetics thrust on the physician by the patient and the lawmaker, it is necessary to keep up as much as possible, if not by actual work, then by reading or otherwise. The style of the author is by no means easy, yet careful reading will disclose many suggestions of value. The medical mind as readily falls into routine as others, and one evidence of this is the acceptance of early evolutionary doctrines as of apodictic certainty. Bateson gives a rude shock to such minds. He begins by a discussion of genetics and the problem of species and varieties, based largely on his previous work on Mendelian principles of heredity. For those who have not followed Bateson's articles in the periodic press, this chapter is full of suggestions and stimulation, though minds that require dogma (in Bateson's words, those not "of first-rate analytical power") will be sadly disappointed. In the chapter on "Meristic Phenomena" many problems that appeal to the pathologist and clinician are touched on—not with finality, but again suggestively, for instance, in regard to twins, transposition, coalescence of digits, polydactylia, etc. In the classification of variations Bateson discusses the causes of acquired characteristics; that is, antibody formation, genius, etc. His views have become well known through other sources and are here clearly set forth. The chapter on the "Mutation Theory" should be studied by all who have floated with the evolutionary tide—not to follow another prophet, but to learn some of the things that still remain unknown. Altogether the work is one of great interest. Medical readers will appreciate it all the more, because in typography and other make-up it is so superior to their usual reading matter.

A TEXT-BOOK OF MEDICAL DIAGNOSIS. By James M. Anders, M.D., Ph.D., LL.D., and L. Napoleon Boston, A.M., M.D. Philadelphia and Boston: W. B. Saunders Company, 1914.

The "Text-Book of Medical Diagnosis" of Anders and Boston is one of the most faulty works on the subject that has ever come to the attention of the present reviewer. One can hardly open it anywhere without finding gross mistakes. The present reviewer has opened it twenty-six times at random, and finds the following twenty-six errors:

On page 101 it is stated that the sputum of bronchiectasis is usually "grayish or brown in color and mucopurulent in consistence." In fact, such sputum is rare in that disease. Pure pus is the rule.

On page 243 we are given, under the heading of "Laboratory Diagnosis of Pericarditis," a summary of the urinary changes seen in any fever, and therefore of no diagnostic value in pericarditis.

The picture on page 259, showing where a thrill was felt under the left clavicle a year after an attack of ulcerative endocarditis, is accompanied by no text which gives us any reason to believe that the ordinary subclavian thrill has been excluded.

On page 283 it is stated that the transmission of a loud mitral regurgitant murmur to the region of the left scapular angle is rare. Yet, on the opposite page, 282, it is stated that this murmur is found posteriorly.



On page 298 it is stated that in typical cases of chronic myocarditis the pulse is slow, from 30 to 60 beats per minute. Clinical observation gives no support for such a statement.

On page 351 primary anemia is wrongly defined as one in which the blood-making organs are affected primarily.

On page 385 it is stated that "drug purpura follows the administration of lethal doses of mercury, belladonna, potassium iodid, ergot," etc. Presumably "lethal" is a mistake for "toxic." Two paragraphs further down arthritic purpura is said to be associated with lesions "of the heart and other serous membranes."

On the next page, 386, it is said quite mistakenly that the blood findings in purpura closely resemble those seen in the various types of secondary anemia. In fact, the blood is usually normal in purpura. At the foot of this page it is stated that purpura of whatever type is always of grave significance; the grounds for such a statement the reviewer cannot conceive.

On page 490 the summary of the diagnostic characteristics of chronic gastritis contains nothing that is in any way peculiar to that disease or diagnostic of it.

On page 492 it is stated that the pain of gastric ulcer begins from one to ten minutes after the taking of food. Clinical experience is united in finding that the pain usually originates much later after the taking of food.

On page 498 it is stated that a lack of success in the attempt to remove fluid from the stomach by means of the stomach-tube is a characteristic feature of hour-glass contraction of the stomach. Of course this feature is not characteristic of hour-glass stomach, since it occurs in a variety of other conditions.

On page 501 it is incorrectly stated that secondary anemia is a constant feature of gastric cancer.

On page 506 it is stated that succussion sounds are to be found over the normal stomach of the negro. The African race enjoys no monopoly of this finding, as would seem to be implied.

On page 598 it is stated that in the early stages of atrophic cirrhosis the liver is somewhat enlarged. Possibly this may be true in some cases, but the reviewer knows of no evidence that bears out such a statement.

On page 624, under the diagnosis of pancreatic cancer, it is stated that the vomitus is "bilious" in character and that the stools contain undigested muscle fibers. In the reviewer's experience neither of these features is of any importance in the diagnosis of that disease.

On page 627 it is mistakenly stated that pronounced enlargement of the spleen is found in tricuspid regurgitation.

On page 734 it is said that the skin of patients with chronic dysentery always feels cool. This is certainly a misstatement. On the same page the presence of tubercle bacilli in the sputum is mentioned as a differential point between chronic dysentery and tuberculous ulceration of the colon. No hint is given of the fact that tubercle bacilli are often found present in the feces despite a normal condition of the intestine.

On page 805 mensuration is said to show deficient expansion of the phthisical chest even in the earliest cases—a remarkable statement. The further description of incipient phthisis corresponds properly with that of *advanced* phthisis, not of the incipient disease.

On page 807 it is stated that all traces of the ophthalmotuberculin reaction disappear from the conjunctivae within two or three days; the cases in which a much more serious conjunctivitis follows are here ignored.

On page 813 it is said that the hemic changes of tuberculosis are those of secondary anemia; there is no hint of the fact that the blood of advanced tuberculosis usually shows no anemia at all.

On page 892, under the etiology of acute articular rheumatism, nothing is said concerning the work of Poynton and Paine, or of Rosenow, on the peculiar

streptococci found by them in rheumatism, and now generally admitted to be the cause of that disease.

On page 894 the ancient fallacy of an "acid sweat" in acute articular rheumatism crops up once more. This is a relic of the old uric acid theory of rheumatism. In fact, the sweat of practically every febrile disease is acid unless the skin is previously cleansed with alcohol.

Under the account of *tabes dorsalis* the reviewer can find nothing about the diagnostic value of lumbar puncture.

On page 1009 occurs a quite antediluvian paragraph on lithemia.

On page 1152 we find myxedema strangely placed among the diseases of the nervous system, and arthritis deformans on page 1158 under the same general caption.

The foregoing twenty-six comments represent the results of opening this book in twenty-six places. The best thing in the book is Dr. George E. Pfahler's section on x-ray evidence in disease of the pericardium, heart and blood-vessels

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## ACTION OF ATOPHAN AND NOVATOPHAN IN GOUT AND IRITIS \*

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Since the work of Nicolaier and Dohrn<sup>1</sup> showing an increased elimination of uric acid, due to the action of 2-phenylquinolin-4-carboxylic acid (atophan), a great deal of work has been done by many investigators with this substance. All get results showing an increased elimination, but all are not in accord in explaining the mechanism by which this increased elimination is obtained. Weintraud,<sup>2</sup> as well as Frank and Bauch,<sup>3</sup> have concluded from results of experiments in which uric acid was injected and sodium nucleinate was fed, that the atophan acts by increasing the efficiency of the kidney for uric acid elimination. Deutsch,<sup>4</sup> Folin and Lyman<sup>5</sup> and Zuelzer<sup>6</sup> have reached the same conclusion by showing a decrease in the uric acid content of the blood, after the administration of atophan. Retzlaff<sup>7</sup> and Brugsch,<sup>8</sup> as well as Gudzent, Klemperer and Dohrn (cited by Retzlaff), were unable to obtain any decrease in the uric acid of the blood by the action of atophan, but, to the contrary, obtained an increase, which they interpret as indicating a mobilizing action of the atophan.

\* Submitted for publication June 26, 1914.

\* From the Laboratory of Physiological Chemistry, Jefferson Medical College.

1. Nicolaier, A., and Dohrn, M.: Ueber die Wirkung von Chinolincarbon-säure und ihre Derivate auf die Ausscheidung der Harnsäure, *Deutsch. Arch. f. inn. Med.*, 1908, xciii, 331.

2. Weintraud, W.: Zur Wirkung der Stophan bei Gicht, *Verhand. d. deutsch. Kong. f. inn. Med.*, 1911, p. 482.

3. Frank, E., and Bauch, B.: Ueber den Angriffspunkt des Atophans bei seiner Einwirkung auf die Harnsäure Ausscheidung . . . *Berl. klin. Wehnschr.*, 1911, xlviii, 1463.

4. Deutsch, F.: Ueber die Wirkung des Atophans bei Gesunden und Gicht-kranken, *München. med. Wehnschr.*, 1911, lviii, 2652.

5. Folin, O., and Lyman, H.: On the Influence of Phenylquinolin Carbonic Acid (Atophan) on the Uric Acid Elimination, *Jour. Pharm. and Exper. Ther.* 1912-13, iv, 539.

6. Zuelzer, G.: Ueber die Diagnose der Gicht durch Atophan, *Berl. klin. Wehnschr.*, 1911, xlviii, 2101.

7. Retzlaff: Ueber Atophan Therapie bei der Gicht, *Deutsch. med. Wehnschr.*, 1912, xxxviii, 404.

8. Brugsch, T.: Diagnose, Wesen und Behandlung der Gicht, *Berl. klin. Wehnschr.*, 1912, xlix, 1597.

It appears to us, however, that although probably the primary action of the atophan is the stimulation of the kidney, for uric acid elimination, yet it is logical to think of at least an indirect mobilizing action. In normal cases and in non-gouty cases the uric acid elimination, under the influence of atophan, is rather large the first day, and falls after a day or two to a point below normal. This is apparently due to the depletion of the supply of uric acid in the blood, and as there are no deposited urates, there is no replenishment of the depleted blood. In the case of gout, however, there are deposits, which may be mobilized, tending to maintain the blood concentration, thus accounting for the rather high and long-continued increased excretion of uric acid in gout cases, as mentioned by Zuelzer.<sup>9</sup> That the mobilization is not extensive is apparently indicated by the fact that the uric acid content of the blood is lower at the end of the atophan treatment. It seems reasonable to think that as the supply of uric acid in the blood is decreased through the action of atophan, there would be a tendency for the solution of the deposits.

In connection with the mobilizing of deposited urates, the work of Daniels,<sup>9</sup> showing an apparent increase in the uric acid output in gout over that due to atophan, by the use of lithium along with atophan, is of interest. Abl† has suggested the use of other drugs with atophan.

Our studies were conducted on patients in the Jefferson Hospital, and in all instances the subjects were placed on purin-free diets. No attempt has been made to give complete clinical findings.

OBSERVATIONS 1 AND 2.—*Gout*.—N. W., aged 20. (Tables 1 and 2). The patient had a marked hypertrophy of the left ventricle, had had several severe dilatations, chronic interstitial nephritis, numerous tophi in the ears, and arteriosclerosis. Blood-pressure was high as a result of the arteriosclerosis.

TABLE 1.—OBSERVATION 1, GOUT

Day	Urine		Blood (100 gm.) Uric Acid mg.	Atophan gm.
	Vol. c.c.	Uric Acid gm.		
1	1,975	0.217		
2	1,625	0.068		
3	2,474	0.087		
4	2,282	0.084		
5	2,064	0.101	2.54	3
6	2,077	0.101	....	3
7	1,805	0.054	1.60 *	3
8	1,216	0.097		
9	1,898	0.127		
10	2,530	0.157		
11	2,438	0.144		
12	2,590	0.121	1.71	

\* Taken at the end of Day 7.

9. Daniels, Amy L.: The Influence of Lithium and Atophan on the Uric Acid Excretion of a Gouty Patient, *THE ARCHIVES INT. MED.*, 1914, xiii, 480.

† Abl: *Arch. f. exper. Path. u. Pharmacol.*, 1914, lxxiv, 119.

TABLE 2.—OBSERVATION 2, SAME CASE AS IN TABLE 1

Day	Urine		Blood (100 gm.)	Atophan gm.
	Vol. c.c.	Uric Acid gm.	Uric Acid mg.	
1	2,182	0.205		
2	1,780	0.161		
3	1,712	0.221	4.88	5
4	1,622	0.208	....	5
5	1,915	0.216	3.44 *	5
6	1,370	0.147		
7	2,280	0.207		

\* Taken at the end of Day 5.

There were no active symptoms of gout during the first observation, but on the morning of the final day, the patient complained of slight soreness in both great toes. The diet was supposedly continued purin-free between the two periods, but the patient received chicken at least once during that time; the exact day he received it, is, however, uncertain.

At the beginning of the second observation, both toes were swollen, inflamed and very painful. At the end of the second day of atophan treatment, the symptoms were much improved. The toes were still swollen, and at the end of the third day were about the same. After the atophan was stopped the symptoms reappeared, although not to the same extent. There was no noticeable change in the tophi, under the atophan treatment, as reported by Richter.<sup>10</sup>

In the "very severe case of gout" cited by Folin and Lyman,<sup>5</sup> the atophan caused neither an increased uric acid elimination nor a diminished uric acid value of the blood, the blood containing the normal amount of uric acid. In our case, although the content of uric acid in the blood was normal, we obtained an appreciable reduction, although the increase in elimination was exceedingly slight. The case is of considerable interest because of the exceptionally low uric acid elimination.

In the case reported by Folin and Lyman, the rise in the uric acid content of the blood seems to be due to the decreased elimination. The increase noted in our case is apparently not to be accounted for in the same manner, as there was an accompanying increase in elimination.

OBSERVATION 3.—*Iritis*.—M. P., laborer, aged 55. Ulcerative keratitis. Patient was attending a brush fire and the wind blew some sparks and smoke into his eye. Previous treatment, atropin after sweats. Sweats discontinued with the start of this experiment. Discharged, much improved.

10. Richter, Paul Friedrich: Ueber Wesen und Behandlungen der Gicht, Deutsch. med. Wchnschr., 1911, xxxvii, 2361.

TABLE 3.—OBSERVATION 3, IRITIS

Day	Urine		Blood (100 gm.) Uric Acid mg.	Atophan gm.
	Vol. c.c.	Uric Acid gm.		
3	1,000	0.263		
4	1,000	0.274		
5	1,000	0.274		
6	(Lost)			
7	1,210	0.293		
8	1,090	0.274		
9	1,000	0.270	1.4	5
10	1,000	0.307	...	5
11	1,090	0.273	0.4 *	5
12	458	0.253		
13	965	0.366		
14	1,000	0.146		

\* Taken at the end of Day 11.

In the table, all urines recorded as 1,000 c.c. volume were very concentrated, and contained sedimented uric acid and urates. These were dissolved in sodium hydroxid and then the whole amount made up to 1 liter with distilled water. The volumes averaged about 300 or 400 c.c.

The iritis seemed to clear up rapidly under the influence of the atophan, although the uric acid elimination was not influenced.

OBSERVATION 4.—*Iritis*.—C. S. aged 35. Had two children, no miscarriages. No venereal infection. Never any acute articular rheumatism. Family history negative. Patient would not remain for the completion of the experiment, and would not permit of the taking of a final blood sample, for no apparent reason, except possibly because of menstruation, which occurred during the course of the experiment.

TABLE 4.—OBSERVATION 4, IRITIS

Day	Urine		Blood (100 gm.) Uric Acid mg.	Atophan gm.
	Vol. c.c.	Uric Acid gm.		
1	1,500	0.297		
2	1,310	0.312		
3	800 *	0.206		
4	760 *	0.135		
5	1,450	0.278		
6	2,010	0.348		
7	1,295	0.317	0.66	5
8	1,005	0.225	....	5
9	1,065	0.169	....	5

\* Probably some of these two samples were lost, although the nurses claimed the samples were complete.

In both cases of iritis (Observations 3 and 4), there was no appreciable increase in the uric acid elimination due to the atophan, although in the first case there appeared to be a slight delayed increase, similar to one recorded by Deutsch.<sup>4</sup> Haskins<sup>11</sup> also noted a delay in the time

11. Haskins, H. D.: The Effect of Atophan and Novatophan on the Endogenous Uric Acid Excretion of Normal Men, Jour. Pharm. and Exper. Ther., 1913, v, 63.



of appearance of the uric acid increase. The explanation for the lack of increase in uric acid excretion in iritis, as well as for the clearing up of the trouble under the atophan, in both our cases, is not apparent. It may be that atophan has an important action totally unrelated to uric acid. May this not be due to the antiphlogistic action of atophan which Starkenstein and Wiechowski<sup>12</sup> have demonstrated? We hope to investigate this point.

OBSERVATION 5.—*Acute Rheumatic Fever and Pericarditis*.—G. R., aged 18. All joints limited in motion. Distinct pain over vertebrae. Right wrist and hip most sensitive. Widal positive. Wassermann negative. Data in regard to history, both personal and family, very indefinite, although there was apparently no family history of gout. Had been receiving ferrosalicylate, and had also received, some time after the salicylate was stopped, 5 gm. of atophan per day for a period of five days. This was stopped the morning our observation period began. He had also received sodium bicarbonate, aspirin, and an occasional hypodermic injection of morphin to relieve pain. The sodium bicarbonate was continued throughout the observation period.

TABLE 5.—OBSERVATION 5, ACUTE RHEUMATIC FEVER AND PERICARDITIS

Day	Urine		Atophan gm.
	Vol. c.c.	Uric Acid gm.	
1	855	0.214	
2	710	0.212	
3	2,385 *	0.501	
4	920 †	0.313	
5	2,025	0.579	5
6	1,370	0.343	5
7	1,590	0.398	5
8	2,005	0.479	5
9	1,800	0.432	5
10	2,230	0.540	5
11	1,515	0.324	
12	2,610	0.596	
13	1,315	0.250	
14	1,825	0.593	
15	1,370	0.607	

\* Patient (without our knowledge) was given two cups of water every half hour during the day, which may explain the large increase in uric acid eliminated, although little is known as to the effect of water ingestion on the uric acid output.

† Patient perspired excessively throughout the day and night.

After the atophan was stopped, previous to the observation period, the patient became worse, the pain increasing, and on Day 3 of the experimental period, patient had a temperature of 102.5. On the administration of atophan, the pain disappeared, and the patient was able to sit up in bed, feeling much improved. There was not a second relapse similar to the first during the time the patient continued under our observation.

12. Starkenstein, E., and Wiechowski, W.: Ueber die Pharmakologie des Atrophaus, Prager med. Wehnschr., 1913.

According to Zuelzer,<sup>6</sup> who finds in all cases of gout a rather marked increase in uric acid output, continued over a long period of time, and in all non-gouty joint affections, a smaller increase over only one or two days, this case would be considered as of a gouty nature. A similar rather high and uniform increased elimination is to be noted in the case of J. S. B., Observation 6, which case was diagnosed as gouty.

The increases of Days 12, 14 and 15 are rather peculiar, and not easily accounted for, unless as a delayed increase from the long atophan period.

OBSERVATION 6.—*Arteriosclerosis and Gout*.—J. S. B., bar-tender, aged 55. Rheumatic pains about shoulders and upper back. Alcoholic. No family history of gout or similar conditions. No previous history of rheumatism or lues.

TABLE 6.—OBSERVATION 6, ARTERIOSCLEROSIS AND GOUT

Day	Urine		Novatophan gm.
	Vol. c.c.	Uric Acid gm.	
1	1,380	0.426	
2	2,565	0.416	
3	1,970	0.384	
4	2,095	0.543	5
5	2,250	0.563	5
6	1,980	0.521	5
7	2,040	0.314	
9	2,245	0.294	
9	1,870	0.391	
10	1,790	0.403	

In this case results, similar to the usual results with atophan, were obtained with novatophan. The patient felt very much better while receiving the novatophan, and the discomfort in the shoulders returned, although not to the same extent, after the treatment was stopped. It is probable that the elimination would not have remained so uniform (see Days 4, 5 and 6) had the administration of the novatophan been continued for a longer period.

In one case in which atophan was given in tablet form, no difficulty was experienced in regard to an unpleasant taste. In the other cases gelatin capsules were used. In no case were there any untoward symptoms, as for example the scarlatiniform rash, noted by Herrick.<sup>13</sup>

Skorczewski and Sohn<sup>14</sup> report that atophan urines respond in the characteristic manner to Ehrlich's diazo reaction. They are substantiated by Dohrn.<sup>15</sup> We were unable to obtain the typical reaction in any

13. Herrick, W. W.: A Scarlatiniform Rash from Atophan, Jour. Am. Med. Assn., 1913, lxi, 1376.

14. Skorczewski, W., and Sohn, I.: Ueber einige in Atophanharnen auftretende charakteristische Reaktionen, Wien. klin. Wchnschr., 1911, xxiv, 1700.

15. Dohrn, Max: Ueber Farbreaktion speziell die Diazoreaktion im Atophanharn, München. med. Wchnschr., 1912, lix, 568.

case. A similar reaction was obtained, but easily differentiated from the characteristic one.

Owing to previous difficulties experienced in the collection of blood samples, the uric acid was not determined in the blood during Observations 5 and 6. In determining the uric acid in blood, we followed slight modifications of the method of Folin and Denis<sup>16</sup> as suggested by Myers and Fine.<sup>17</sup> The oxalated blood was poured into about four volumes of boiling distilled water, with stirring, and again brought to a boil. Hundredth-normal acetic acid was then added to complete coagulation, about an equal amount being required. The procedure from this point on was the same as the original. In all cases (both blood and urine) three drops of concentrated hydrochloric acid, instead of one drop as called for by the method of Folin and Denis<sup>18</sup> were added along with the hydrogen sulphid used to decompose the silver urate.

We wish to express our indebtedness to Drs. McCrae, Solis-Cohen, Hansell and Sweet of Jefferson Hospital for permission to study the cases herewith reported. We are also indebted to Drs. Burns, Clerf, Dry, Livengood, Lummis, Shannon, and Wayland, as well as the nurse in attendance, for care and assistance in the collection of blood samples and the handling of the cases.

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16. Folin, O., and Denis, W.: A New (Colorimetric) Method for the Determination of Uric Acid in Blood, *Jour. Biol. Chem.*, 1913, xiii, 469.

17. Personal communication.

18. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1913, xiv, 95.

# THE RADIO-ACTIVITY OF THE MINERAL WATERS OF HOT SPRINGS, WARM SPRINGS AND HEALING SPRINGS IN HOT SPRINGS, VA.\*

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BALTIMORE

The study of radium and radio-activity long ago became a subject of great interest, not only for the pure scientist, but also for the physician and his patients. The search for radium-containing ores in this country, while it has been successful in demonstrating the wealth contained in the earth, has also evidenced the great scarcity of this metal. It is important, therefore, to study the numerous springs of this country in the light of their radio-activity. Although the analyses made in this country are not numerous, it is to be hoped that in the course of years the contributions to our knowledge of the radio-active properties of our springs will become more numerous. It is with this aim that the following investigations were undertaken. Before detailing the results of these investigations, a few historical facts may be pertinent.

Since the discovery of the "x-rays" by Roentgen<sup>1</sup> in 1895, numerous scientific facts have been revealed; for example, the Becquerel or the "canal" rays of Goldstein (1898), the radio-active properties of uranium, the isolation of polonium and radium (Schmidt and Madame Curie,<sup>2,3</sup> Giesel,<sup>4</sup> Marckwald<sup>5</sup>), of thorium (Hahn<sup>6</sup>), of actinium (Debierne,<sup>7</sup> 1899), the ekalathan (by Giesel<sup>8</sup>) and the radiothor (by Marckwald in 1902). The study of the chemical and physical properties of these substances and of the products resulting from their continuous disintegration, led to the discovery of different rays (alpha, beta, gamma), to whose action the chemical-biological effects of radio-active substances must be attributed.

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\* Submitted for publication May 5, 1914.

1. Cited according to Rutherford: *Radioactive Substances and Their Relations*, 1913, p. 6.

2. Curie, P. and S.: *Compt. Rend. de l'Acad. d. Sc.*, 1898, cxxvii, 1215. Curie M. and Mme., and Bemont, G.: *Compt. Rend. d. l'Acad. d. Sci.*, 1898, cxxvii, 1215.

3. Hampson: *Radium Explained*, p. 20.

4. Giesel: *Ann. d. Physik.*, 1890, lxi, 91; *Ber. d. deutsch. Chem. Gesellsch.*, 1902, p. 3608.

5. Marckwald: *Physikal. Ztschr.*, 1903, iv, 51. *Ber. d. deutsch. Chem. Gesellsch.*, 1903, p. 2262.

6. Hahn: *Proc. Roy. Soc.*, 1905, lxxvi, 115; *Phys. Ztschr.*, 1907, viii, 277; *ibid.*, 1908, ix, 392.

7. Debierne: *Compt. Rend. de l'Acad. d. Sc.*, 1899, cxxix, 593; *ibid.*, 1900, cxxx, 206.

8. Giesel: *Ber. d. deutsch. Chem. Gesellsch.*, 1902, p. 3608; *ibid.*, 1903, p. 342.

Besides these different rays, emanation was discovered as a constant decomposition product in connection with radium and thorium, as well as in actinium (1900 Dan). The emanation, a gas of an evanescent character, diffuses rapidly into the surrounding air and is readily dissolved in water, and in contact with other substances the radio-active properties of this emanation are imparted to the former, so creating excited (induced) radio-activity. Emanation that contains alpha rays is radio-active and as such ionizes the air. As a gas it is subject to the laws of diffusion and is condensed at a temperature of minus 185 C. Its qualities can be preserved in a latent stage (Ebert,<sup>9</sup> Rutherford and Soddy<sup>10</sup>). The atomic weight of emanation, according to Ramsay<sup>11</sup> and Sommer,<sup>12</sup> is 218.5; its half-time or half-value (that is, in that time the substance will have lost 50 per cent. of its original strength of radiation) is 3.8 days. Dry emanation under considerable heat rapidly splits up and produces helium. Moist or dissolved in water, the decomposition product is called neon (atomic weight 20). In the presence of copper salts argon (atomic weight 40) is formed. Elster and Geitel<sup>13</sup> were the first to detect the frequency of emanation as present in the air, in the soil, in caves, in the atmospheric precipitations (rain, snow). In England, G. Thompson<sup>14</sup> in Cambridge, in Italy, Pocchettino and Sella in Rome,<sup>12</sup> demonstrated radio-activity and radio-emanation in the air and in the waters. Since 1903 these facts have been confirmed by numerous investigators (Thompson, Allen, Himstedt,<sup>15</sup> Lord Blytheswood, Strutt, Elster and Geitel,<sup>13</sup> Dom, Schenck, Mache). A review of the literature on radio-activity of mineral waters, and of the by-products and sediments found in spas, would certainly be of interest, but would surpass the aims of the present paper. It seems, however, that the most numerous contributions in this line have been carried out by German and Austrian investigators, so that the most renowned spas can be compared with regard to their radio-activity (Joachimstal, Brambach, Gastein, Lacco Ameno (Ischia), Carlsbad, Baden-Baden, Baden b. Wien, Teplitz, Nauheim, Marienbad, Franzensbad Dürkheim, Kreuznach, Muenster, Landeck in Silesia and others).

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9. Ebert: *Ber. d. Bayr. Acad. d. Wissensch. München.*, 1903, xxxiii, 1333.

10. Soddy: *The Interpretation of Radium*, 1912.

11. Ramsay: *Jour. London Chem. Soc.*, 1907, xci.

12. Sommer, in *Emanation and Emanationstherapie* (Gmelin), 1909.

13. Elster and Geitel: *Phys. Ztschr.*, 1900, i, 11; *ibid.*, 1901, ii, 116, 560, 590; cited by Rutherford (Footnote 1, p 340); Engler and Sieveking: *Radium in Biol. u. Heilk.*, 1912, i, 277.

14. Cited according to Rutherford (Footnote 1, p. 641).

15. Himstedt: *Ann. d. Phys.*, 1903, xii, 107; *ibid.*, 1904, xiii, 573; cited by Engler and Sieveking (Footnote 13, p. 270).

## METHODS OF THE DETERMINATION OF RADIO-ACTIVITY

For the determination of radio-activity of fluids, gases, sediments and stones, different methods have been recommended, such as:

(a) The test on the fluorescent screen as compared with standard radium preparations.

(b) The action on the sensitized photographic plate, as compared with standard radio-active compounds.

(c) The measurement of the ionized air, produced by the emanation contained in radio-active fluids, solids and gases.

The latter method is the one most frequently used and gives good results. This can be done as follows:

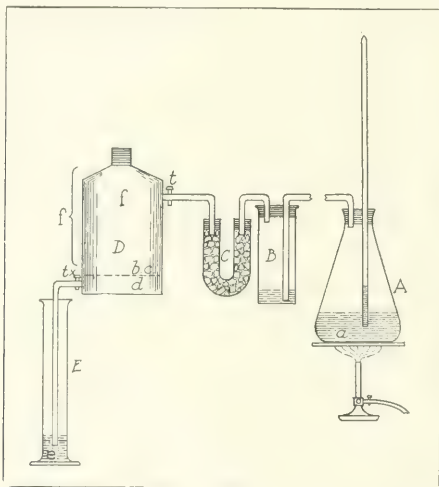


Fig. 1.—Diagram of apparatus for testing the radio-activity of dissolved and gaseous emanation in spring waters: A, flask; B, wash-bottle; C, absorption tube; D, Gas tank; E, measuring-glass; t, tx, taps; a, mineral water; b, normal loss for ordinary tap water; d, radio-activity of remaining tank water after passage of gas; e, radio-activity of escaped water from tank; f, radio-activity of gas mixture in tank.

1. By circulating the emanation through the electroscope. By pressure the emanation is liberated from the water and then reaches the electroscope by a closed system. In this apparatus the charged leaflets of the electroscope lose their electric charge more or less rapidly, according to the ionization of the air containing the emanation. By means of a microscope the rapidity and the distance of the leaflets is read off from a scale. Such a method was first recommended by



Elster and Geitel<sup>16</sup> and has been used since by different investigators — Boltwood,<sup>17</sup> Schlundt and Moore,<sup>18</sup> and others. Different causes of error have to be eliminated; for example, the rubber connections and the glass tubing can absorb the emanation, or the mechanical propulsion may be at fault and thus an irregular circulation of the emanation may result. Instead of forcing air through the fluid, which drives off the emanation, the radio-active water can be boiled. In this manner the emanation escapes rapidly and can be measured in the electroscope. This method gives some higher values than the one previously mentioned. If sediments or minerals are to be examined, these are either dried or calcinated and the emanation that escapes can be collected and measured.

2. Engler and Sieveking<sup>19</sup> adopted another manner of procedure which is as follows: The water, under the necessary precautions, is poured into a given tank, and after hermetic closure by a well-fitting rubber stopper, is shaken vigorously for one-half to one minute. If the mineral water should contain a considerable amount of free carbonic acid, this chemical substance, freed from the water, increases the pressure in the tank. Occasionally the rubber stopper may be blown off and with it a considerable loss of emanation may result. To avoid such an accident a small amount of water is allowed to escape through a small tap at the bottom of the tank, without any gas, in order to restore the normal pressure. By shaking the water the emanation is driven into the air, and only about 2 per cent. of the original amount remains dissolved in the fluid. The fontactoscope from Engler and Sieveking is the apparatus most frequently used in the tests reported in the literature, for comparative measurements with this method gave results as close to those control tests as could be obtained by any other laboratory method. In our investigations we also used the fontactoscope of Engler and Sieveking, the dispersion factor of the apparatus being indicated as 13.8. The technic which we followed was, in brief, as follows:

1. Determination of the electric conductivity of the tank containing ordinary air, ascertained by successive reading of the distance of both leaflets of the electroscope during one hour. Each fraction of the scale corresponds to a certain electric tension in volts, and so the normal loss for each determination was ascertained. According to the time of the day, the weather, the humidity of the surrounding air, this normal loss differed from the previous determinations. In cases in which the figures obtained were high, owing to the accumulation of humidity in the apparatus, the air was dehydrated by the introduction of a small amount of metallic sodium left in the capsule of the electroscope. After this the normal loss became smaller.

16. Elster and Geitel: *Phys. Ztschr.*, 1905, v, 32.

17. Boltwood: *Am. Jour. Sc.*, 1904, Series 4, xviii, 97; 1905, xx, 128.

18. Schlundt and Moore: *U. S. Geol. Survey*, 1909, *Bull.* 315.

19. Engler and Sieveking: *Radium in Biol. u. Heilk.*, 1912, i, 277.

2. Determination of the radioactivity of the normal mineral water. After a qualitative test had demonstrated the presence of radio-activity in the water, a measured quantity of the water was collected from the spring under the proper precautions in a hermetically closed glass container, transferred as quickly as possible to the laboratory; immediately placed in the gas tank, shaken for one-half to one minute, the electroscope rapidly adapted, charged with positive electricity and the first reading of the distance of the leaflets taken. A stop-watch marked the fractions of minutes, and at regular intervals, as recorded on the tables, the distance of the leaflets was ascertained. In most instances the highest readings were obtained in one-half minute from the beginning of the experiment. The readings were continued up to an hour or even longer. These figures, representing the distance of the leaflets, correspond to so many volts as indicated in the table, and warranted by the manufacturer of the instrument. After deduction of the normal loss of tension as found for air, these figures then were computed for one liter and for one hour's time, and the volt-hour pro liter mineral water was found. In most of the results published by other investigators we find the radio-activity rendered in electrostatic units,

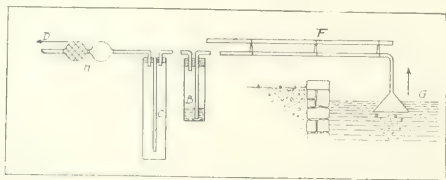


Fig. 2.—Method of collecting the escaping gas from the spring for the examination of radio-activity: F, stick supporting funnel, G, which is connected with the wash-bottle, B, the dehydrating tube, C, and the aspiration bulb, H.

or, as these figures usually are exceedingly small, this product multiplied by 1,000 is quoted as Mache units (M.-U.). In our tables the values correspond to Mache units per liter water and per hour. For our purposes no corrections, as for the induced radio-activity formed in the gas tank, or the residual activity as contained in the remaining water, were made. Such corrections amount to a few Mache units only in the average cases and they would not change materially the results obtained. In each determination of the radio-activity of mineral water a normal test preceded, and that was made after careful washing of the gas tank with ordinary tap water so that any remaining induced activity could be excluded. For therapeutic purposes a small difference in Mache units can hardly be of great importance.

In the progress of our investigation we were impressed by the observation that even in taking the greatest precautions a loss of emanation could not be prevented; even then when we did not lose any time before the determinations were begun. This observation was strengthened by the marked difference in the results of the determination of Healing Springs and of Warm Springs. In both instances the samples determined in the laboratory and the readings taken immediately at the spring itself, demonstrated the superiority of the field determinations (differences from 84.7 to 90.8 per cent.), provided favorable meteorological conditions prevailed. Several field tests at the source were carried out and accordingly more accurate readings were

obtained. After each determination of mineral water the tank was carefully washed out with ordinary tap water in order to remove the induced radio-activity adhering to the walls of the gas tank. In some of the tests the mineral water was left for a given time in an open or closed jar and then the radio-activity ascertained. In some instances in the closed jar the emanation collected still showed high values. Further observation, however, revealed, by the quick loss, that most of the ionization of the air was due to emanation gas and not to radio-active substance in solution.

In some springs the amount of dissolved emanation was ascertained by boiling a given amount of mineral water. The following description may help to an understanding of the procedure:

Flask A (Fig. 1) is provided with a long glass tube ending in a fine capillary point (to avoid over-pressure by the escape of air), the lower end reaching to the bottom of the flask. Connected with the boiling flask is the wash-bottle B, to retain any impurities that might be driven over from A. In connection with B is the absorption tube, C, filled with calcinated calcium oxide, for the absorption of humidity and vapors. Glass and rubber tubing connect C with the gas tank D, provided with several taps, *t*, and *tx*, and a well fitting rubber stopper at the top. Connected with the gas tank through the tap, *tx*, is the measuring glass, E, to receive the escaping water from the gas tank.

Previous to the testing of the dissolved radio-activity of the mineral water the following determinations are necessary: (1) Conductivity of the gas tank filled with air. (2) Conductivity of the ordinary tap water with which the tank is to be filled to the brim. After these values have been obtained, a given amount of mineral water (*a*) is boiled for five minutes in the flask A, then the tap, *t*, is opened and also *tx*; slowly the water is emptied from the gas tank, D, and measured in the receiving vessel, E, and a certain amount of it, *e*, tested for its radio-activity. A slow suction is maintained by the outflowing water and this is continued until eight liters of water escape, leaving only about two liters of water in the tank D (the radio-activity of which is also later ascertained (*d*); the remaining quantity (*f*) constitutes the air and emanation aspirated from the system of containers (A, B, C). The determination of the radio-activity of the air and fluid in tank D is not started until the taps *t* and *tx* are closed and after the gas tank has cooled down to room temperature.

For the computation of the result all these findings are taken into consideration. For example, the degree of radio-activity is ascertained as follows: (1) radio-activity of the collected gas in tank D =  $f - b$  (normal loss of air); (2) radio-activity of remaining tank water =  $d - b$  (normal loss of air); (3) compared with radio-activity of the same amount of ordinary tank water =  $c - b$ ; (4) radio-activity of the outflowed water in the receiving tube, E, =  $e - b$  (normal loss of air). The total value of the computation consisted of  $1 + (2 - 3) + 4 = (f - b) + [(d - b) - (c - b)] + (e - b)$  the value of which was found higher than if only  $D = (f - b)$  was considered.

As seen from the different tables from different springs a given amount of mineral water was evaporated to dryness and then the salt residue tested for its radio-activity. In almost all instances a low conductivity could be ascertained, from which fact one may conclude that in the springs most of the radio-activity must result from the dissolved emanation gas.

FIGURE 3

FIGURE 6

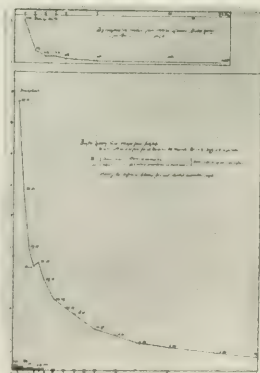


FIGURE 5

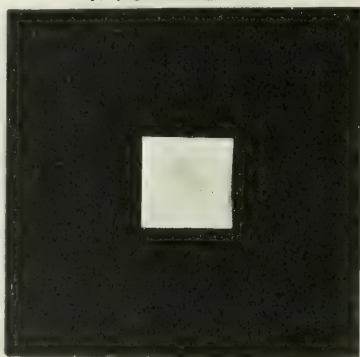


FIGURE 4

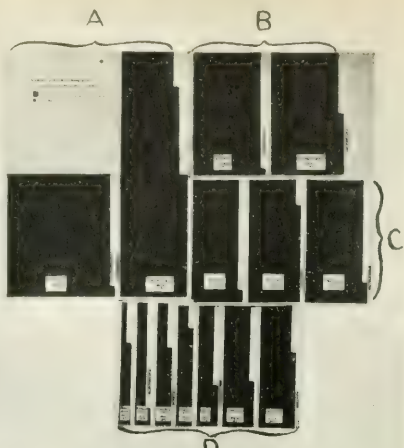


Fig. 3.—Chart representing a comparison of the radio-activity of the different springs at Hot Springs, Warm Springs and Healing Springs at Hot Springs, Va., per liter and per hour in Mache units.

Fig. 4.—Graphic representation of the radio-activity of springs at Hot Springs, Va., in Mache units in a full bath of 200 liters (50 gal.): A (from left to right), Boiler Spring, 48,219.66 M. U.; Magnesia Spring, 56,918.3 M. U.; B, Open Well, 31,326.84 M. U.; Hot Sulphur Spring, 31,562.2; C, Swimming Pool, 21,855 M. U.; Thermal Water, August Spring, 22,503.3 M. U.; Warm Springs, 26,800.5 M. U.; D (from left to right), Spout Spring, 4,207.2 M. U.; Octagon Spring, 5,136.6 M. U.; Cold Spring (north), 6,338 M. U.; Club House Spring, 6,631.9 M. U.; 102 T. Spring, 8,017.2 M. U.; Soda Spring, 12,906.7 M. U.

Fig. 5.—Represents the difference between the radio-activity of the swimming-pool at Warm Springs (white field in center) and the swimming-pool at Hot Springs (black square). The squares are drawn to a scale of 100 Mache units.

Fig. 6.—Chart showing in the upper curve the radio-activity of the dry substance of 1,000 c.c. of Boiler Spring water. The lower diagram refers to the radio-active gas escape of the same spring measured alone and indicated by the heavy columns at the bottom of the chart, and the dissolved emanation found in the tank water, represented by the curve above.

A few tests were also carried out to determine the radio-activity of the gases escaping directly from the springs. For a better comprehension of the method adopted the following description may be useful:

The arrangement of the apparatus (Fig. 2) does not differ much from that previously described. Instead of the boiling flask a rubber and glass tube, suspended on a long stick, F, has as its opening a funnel, G, which is held in direct contact with the water surface, exactly over a spot where the gas bubbles arise from the bottom of the spring. Between the gas tank, D, and the dehydration tube, C, if necessary a rubber aspiration bulb, H, is inserted through

TABLE 1.—COMPARISON WITH SOME EUROPEAN SPAS OF THE DIFFERENT SPRINGS EXAMINED AT HOT SPRINGS, HEALING AND WARM SPRINGS, VA., AS TO THEIR RADIO-ACTIVITY, AND THEIR STRENGTH PER ONE FULL BATH (50 GALLONS 200 LITERS)

Spring	Temp. F.	Water	Gas	Dry Residue	Total	Dissolved Emanation	Per Full Bath—M. U.	Compares with
1	102	16.551	2.012	2.474	21.037	54.676	4,207.256	Neundorf a. Soden.
2	99.0	4.889	12.832	7.062	25.683	3.399	5,136.642	Muenster Nauheim.
3	62.5	31.691	.....	.....	.....	.....	6,348.32	Nauheim.
4	102.5	33.16	.....	.....	.....	.....	6,631.972	Higher than Nauheim.
5	102.0	15.799	21.128	3.160	40.086	18.002	8,017.292	Higher than Nauheim.
6	75.0	64.534	?	?	?	.....	12,906.756	Higher than Kreuznach; less than Baden-Baden.
7	84.0	69.621	13.335	3.513	86.47	80.419	16,083.788	Between Kreuznach and Baden-Baden.
8	63.25	92.63	?	?	?	?	18,526.252	
9	81.5	109.273	.....	.....	.....	.....	21,855.467	
10	73.0	112.517	.....	.....	.....	.....	22,503.384	Little less than Baden- Baden.
11	96.3	95.72	32.41	5.87	134.002	.....	26,800.592	Higher than Baden- Baden.
12	90.25	156.63	.....	.....	.....	.....	31,326.836	Higher than Gasteln.
13	99.4	101.87	54.94	1.22	157.811	75.60	31,562.228	Higher than Gasteln.
14	104.0	86.54	162.18	2.38	241.198	66.234	48,219.669	Higher than Gasteln and Landeck.
15	98.2	260.95	21.52	2.14	284.592	61.06	56,918.3	Higher than Landeck.

The highest radio-activity in swimming-pools (so far as our knowledge goes) is found in the Warm Springs swimming-pool, exceeding the values found in the Radium Kurhaus at Joachimsthal and represented by the figures found at Brambach (Voigtland).

Name of Springs examined: No. 1. Spout Spring; 2. Octagon Spring; 3. North Cold Spring; 4. Club-Spring; Casino Spring; 5. 103° T. Spring; 6. Soda Spring; 7. Healing Springs; 8. South Cold Spring; 9. Swimming Pool at Hot Springs; 10. August Spring (Thermal Water); 11. Warm Springs; 12. Pipe Spring (open well); 13. Hot Sulphur Spring; 14. Boiler Spring (used in bath-house); 15. Magnesia Spring. The numbers of the different springs correspond to those indicated in the tables.

which, by gentle pressure, the gas escaping far below the surface of the spring may be aspirated. The arrangement of the wash-bottle, B, the gas tank, D, and the recipient, E, is just the same as in Figure 1 and the entire technic is carried out as already described. In making the tests about 8 liters of water were withdrawn from the gas tank, D, taps t and tx were closed and the entire apparatus was then hurried to the laboratory, where the different determinations followed immediately. (See preceding determination of gas emanation). At Healing Spring and at Warm Spring the gas tests were made immediately at the spring. Also was the air in the bath cells of Hot Springs collected in a similar way, after securing a hermetic closure of all the outlets of the bath cell. The necessary corrections (as mentioned) were considered in the computation of the final results.



## COMPUTATION OF THE READINGS

As already mentioned, the tension in volts calculated from the readings can be tabulated in a variety of ways. For mineral waters the Mache unit for one liter of water for one hour has been adopted, or the electrostatic unit (1/1,000 Mache units). Another method would be the comparison with the emanation resulting from the saturation current of 1 gram of radium ( $5.3 \times 10^{-5}$  electrostatic units), corresponding

TABLE 2.—TESTS OF RADIO-ACTIVITY MADE ON BOILER SPRING WATER. TEMPERATURE 104 F.

Time Min.	1		2		3		4		5	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	4,779.4	60.70	951.6	12.09	939	11.93	11,982.5	152.18	6,862.5	87.15
1	5,239.86	54	711.6	9.04	759	9.34	9,899.9	125.73	4,638.0	58.90
1½	3,699.4	46.98	671.0	8.53	...	...	9,568.0	86.55	3,199.5	40.63
2	3,299.4	38.14	611.6	7.78	468	5.94	6,588.6	83.29	2,670.7	33.92
2½	3,003.4	38.14	.....	.....	...	...	6,306.52	80.09	2,670.7	33.92
3	2,739.4	34.79	511.6	6.50	499	6.35	5,687.92	72.24	2,345.0	29.78
4	1,289.4	16.38	381.6	4.85	444	5.64	4,928.14	61.59	1,819.8	23.17
5	1,971.4	25.04	302.6	3.84	399	5.07	7,935.36	1,006.78	1,651.2	20.97
6	1,639.4	20.82	291.6	3.7	...	...	4,087.82	51.81	1,457.75	18.51
8	112.15	1.42	254.1	3.03	...	...	3,608.84	45.83	1,073.6	13.63
10	101.8	1.29	225.6	2.87	213	2.71	3,389.38	43.05	898.05	11.41
12	91.9	1.17	186.6	2.37	...	...	3,162.92	40.27	717.5	9.11
15	69.8	0.89	183.6	2.33	155	1.97	3,005.2	38.17	596.0	7.57
21	53.63	0.68	.....	.....	123	1.56	3,073.06	38.26	457.05	5.80
30	67.0	0.47	123.6	1.57	...	...	2,673.16	33.85	359.0	4.56
60	.....	.....	123.6	1.57	...	...	.....	.....	.....	.....

## EXPLANATION TO TABLE 2

1. Test carried out at the spring, avoiding transport of the water; values given in volts and Mache units per hour and test 1,000 c.c. net, after deduction of the normal loss for air in the tank.

2. Same water taken under all precautions but determination made upstairs in the radiological laboratory of the bath-house (loss of time necessarily involved four to five minutes).

3. Boiler Spring water allowed to stand for twenty-two hours in closed jar; notice the remarkable difference in the determination compared with 1 and 2.

4. Gas radio-activity escaping from Boiler Spring, collected under precautions described in text; 2,500 c.c. in twelve minutes; values given for radio-activity of tank water and tank air combined, as the tank water readily absorbs the radio-emanation; more than 90 per cent. (97 to 98 per cent.) is found in the water, whilst the air mixture contains a small percentage of radio-emanation (see Fig. 6).

5. Boiler Spring allowed to flow in bath-tub during twelve minutes and twenty-four seconds; then sample of air collected from the bath-cell, all windows, doors and possible outlets being kept closed during that time. Aspiration of air begun 2 minutes after start of experiment; 2,000 c.c. of water subtracted from water tank during aspiration of about 5,450 c.c. of air.

Emanation total from tank air, in residual and escaping tank water.

to 0.57 c.c. of emanation (Curie and Duane<sup>20</sup>), or one Curie, or fractions thereof (millicurie or microcurie  $\times \frac{1}{10^{-6}}$ ). By comparison of the apparatus with standard radium solutions, or indirectly by computation, the Mache units can always be found (1 Mache unit =  $37.7 \times 10^{-10}$

20. Curie and Duane, cited by Ebler, E.: Ztschr. f. anorgan. Chemie, 1911, lxxii, 243.



Curie). The substitution of a scientific measure by a term selected in memory of a celebrated person may be justified as a reason of acknowledgment, but it presents certain inconveniences; it is preferable, therefore, to use mathematical measures whenever they are possible. It has been suggested (Engler and Sieveking<sup>21</sup>) to adopt as unit the electromagnetic amount of the current, and by multiplication of the figure found by one billion ( $10^{12}$ ) to avoid small figures.

TABLE 3.—TEST OF NO. 13, HOT SULPHUR SPRING. TEMPERATURE 99.4 F. PER 1,000 C.C.

Time Min.	6		7		8		9		10		11	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	139.6	1.77	.....	.....	8,013.2	101.88	6,950.7	88.81	2,733.2	34.7	..	....
1	109.6	1.39	159.2	2.02	5,013.2	63.67	4,010.7	51.47	1,713.2	21.8	96	1.22
1½	67.6	0.86	.....	.....	4,893.2	62.14	.....	.....	1,213.2	15.4	..	....
2	46.6	0.59	45.	20.57	3,893.2	50.71	2,390.7	30.90	.....	.....	36	0.46
2½	46.0	0.58	.....	.....	4,269.2	54.22	2,006.7	26.02	.....	.....	..	....
3	49.6	0.63	23.2	0.29	3,673.2	46.65	1,850.7	23.94	693.2	8.8	16	0.20
4	33.1	0.42	21.2	0.27	2,563.2	32.55	1,520.7	19.85	.....	.....	6	0.07
5	29.2	0.37	12.8	0.16	2,253.2	28.62	1,214.7	16.96	477.2	6.1	48	0.61
6	21.6	0.27	.....	.....	2,043.2	25.95	1,010.7	13.37	.....	.....	..	....
8	20.3	0.26	.....	.....	1,690.7	21.47	755.7	10.13	.....	.....	..	....
10	14.8	0.19	6.2	0.08	1,521.2	19.32	626.7	8.50	297.2	3.8	54	0.69
12	8.0	0.10	.....	.....	1,318.2	16.74	.....	.....	.....	.....	..	....
15	13.2	0.17	3.6	0.05	1,113.2	14.14	450.7	6.25	237.2	3.0	52	0.66
20	11.2	0.14	0.5	0.01	930.2	11.81	362.7	5.14	192.2	2.4	..	....
20	8.0	0.10	.....	.....	633.2	8.04	282.7	3.59	.....	.....	..	....

## EXPLANATION TO TABLE 3

6. Air in the bath-cell; values if only the air in the tank is considered without the determination of the radio-activity absorbed in the tank water.

7. Radio-activity of dry residue obtained after evaporation of 1,000 c.c. of mineral water.

8. Hot Sulphur Springs: Field test of radio-activity per 1,000 c.c.

9. Test of water determined at the laboratory, after collection of water under all precautions, and under minimal loss of time. Transport of water from spring to laboratory in a well closed glass jar, emphasizing the importance of using the water directly at the spring itself.

10. 1,000 c.c. of the same water are allowed to stand over night, and about fourteen hours later the test is carried out; considerable loss is noted.

11. Determination of radio-activity in dry evaporated residue obtained from 1,000 c.c. of Hot Sulphur Spring water.

With regard to the unit to be used in gases, no international unit has been adopted as yet. Several authors (Sommer,<sup>12</sup> Engler and Sieveking<sup>21</sup>) reject the Mache unit as unsuitable. They suggest to simply use the strength of the saturation current in electrostatic or electromagnetic units, or with the proper mention of the apparatus used, to quote simply the loss of volts per hour, or, still better, the number of ions as contained by dividing the saturation current by the amount of electricity carried by an electron (1 c.c. equals 242 ions).

21. Engler and Sieveking: Ztschr. f. anorg. Chemie, 1907, p. 53.

Further, according to P. Curie and Laborde,<sup>22</sup> the milligram minute has been chosen as the unit for the radio-activity of springs. (One milligram minute equals 141 Mache units; one milligram second 2.6 Mache units, Engler and Sieveking, Loewenthal.)

For sediments the factor with which the loss of volts has to be multiplied is smaller. This is based on the experience, that, according to humidity, porosity, etc., of the substance to be examined, the loss of emanation is considerably smaller.

TABLE 4.—TESTS MADE ON MAGNESIA SPRING, TEMPERATURE 98.2 F.

Time Min.	12		13		14		15		16		17	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	14,746.9	188.29	2,135	27.11	506.7	6.44	.....	.....	4,807.8	61.04	2,108.9	26.75
1	20,546.9	260.945	1,175	14.92	1,694.1	21.52	93.2	1.17	11,970.3	151.01	1,808.9	21.96
1½	7,586.9	94.25	775	9.84	1,300.7	16.52	.....	.....	8,674.1	111.29	1,188.9	20.60
2	5,956.9	75.65	650	8.26	931.6	11.93	168.2	2.14	7,326.6	93.05	998.9	12.69
2½	4,954.9	62.93	.....	.....	1,215.1	15.43	.....	.....	5,745.4	62.97	.....	.....
3	4,306.9	54.70	425	5.40	1,086.5	13.75	103.2	1.31	5,698.6	72.37	818.9	10.40
4	3,304.9	41.93	307.5	3.91	889.8	11.30	100.7	1.28	4,779.8	60.7	818.9	10.40
5	2,734.9	34.73	269.0	3.41	846.6	10.75	85.2	1.08	4,122.9	52.36	800.9	10.17
6	2,276.9	28.92	240.0	3.05	652.3	8.28	.....	.....	3,829.8	48.64	828.9	10.53
8	1,771.9	22.50	173.7	2.11	664.5	8.44	66.2	0.84	3,242.9	41.19	811.4	10.30
10	1,468.9	18.66	149.0	1.89	608.4	7.73	.....	.....	2,833.7	36.99	806.9	10.25
12	1,266.9	16.09	.....	.....	575.2	7.31	.....	.....	2,553.2	32.42	773.0	9.83
15	1,098.9	13.96	.....	.....	521.2	6.62	61.2	0.78	2,308.6	29.32	744.9	9.46
20	989.9	12.57	.....	.....	469.5	5.95	.....	.....	2,062.7	26.1	761.9	9.58
30	688.9	8.75	.....	.....	467.7	5.84	.....	.....	770.9	9.79	*	.....

\* Value for water alone, as in the determination of the gas alone, the leaflets of the fontactoscope fell together and the reading could not be carried on further.

## EXPLANATION TO TABLE 4

12. Field test carried out immediately at the spring, avoiding any loss of emanation.

13. Water collected under all precautions, but examined at the radiological laboratory at the Bath-house after about 4½ minutes had passed until the first reading could be made; a considerable difference in the readings is noticed. Added to this must be the time of shaking the tank, the charge of the electroscope with positive electricity (beta-rays). The first reading in No. 13 resembles that made 6 minutes after the beginning of Experiment 12.

14. Determination of gas absorbed directly over the spring; about 2,000 c.c. gas with 1,020 c.c. water contained in the tank (values for gas and tank water combined).

15. Radio-activity in dry residue from mineral water, 1,000 c.c.

16. Emanation collected from 1,000 c.c. of mineral water after heating 1,785 c.c. of gas and 1,100 c.c. of remaining tank water (values combined from both determinations.)

17. Magnesia Spring determination of gas radio-activity alone, showing always a smaller amount than found in the tank water (compare with No. 16).

## DISCUSSION OF RESULTS

With regard to the frequency of radio-activity in water and the recommendation of such waters for therapeutic purposes, where the content of radio-active substances is small in waters having any action

22. Curie, P., and Laborde, cited by Engler and Sieveking (Footnote 21).

whatsoever, von Noorden's suggestion is justified, i. e., a classification of such springs as follows:

1. Weak radio-active waters containing between 25 and 50 Mache units per liter and per hour ( $1,250$  to  $2,500 \times 10^{-11}$  gram radium).

2. Medium radio-active waters, from 50 to 100 Mache units per liter and per hour ( $2,500$  to  $5,000 \times 10^{-11}$  gram radium).

3. Strong radio-active waters, from over 100 Mache units per liter and per hour or over ( $5,000 \times 10^{-11}$  gram radium).

TABLE 5.—TESTS OF HEALING SPRINGS. TEMPERATURE 87 F.

Time Min.	18		19		20		21		22		23	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	5.482	69.62	543.9	6.91	.....	....	276.6	3.51	.....	.....	6,332.2	80.42
1	3.982	50.57	397.3	5.04	259.4	3.29	126.6	1.61	1,050.0	13.33	4,096.4	52.03
1½	3.522	44.73	260.8	3.32	.....	....	.....	....	.....	.....	.....	....
2	2.902	36.87	.....	....	99.4	1.26	111.6	1.42	681.9	8.71	2,335.2	29.66
2½	2.506	31.83	254.5	3.23	.....	....	.....	....	518.2	6.58	.....	....
3	2.262	28.73	250.3	3.18	159.4	2.02	66.6	0.84	542.5	6.89	1,953.8	24.81
4	1.905	23.71	182.0	2.31	174.4	2.21	66.6	0.84	331.6	4.21	1,549.4	19.68
5	1.534	19.48	172.6	2.09	195.4	2.47	.....	....	432.9	5.50	1,305.2	16.58
6	1.322	16.79	139.5	1.80	139.5	1.80	66.6	0.84	390.5	4.96	.....	....
8	1.102	14.00	102.3	1.30	.....	....	.....	....	142.8	1.70	832.4	10.57
10	.952	12.09	71.4	0.89	141.4	1.80	54.6	0.69	351.0	4.56	811.0	10.30
12	.....	....	.....	....	.....	....	.....	....	.....	....	.....	....
15	.674	8.56	48.4	0.61	103.4	1.31	56.6	0.72	.....	....	.....	....
20	.550	6.99	46.4	0.59	99.4	1.26	.....	....	.....	....	.....	....
20	.424	5.38	.....	....	.....	....	.....	....	.....	....	.....	....

EXPLANATION TO TABLE 5

18. Field test immediately at the spring.  
 19. Sample of water taken to the laboratory at Hot Springs under observation of all precautions (lapse of time about one hour; return by automobile). A great difference will be noticed between Nos. 18 and 19.  
 20. Sample of water determined next day, still radio-active but less than previously.  
 21. Radio-activity of dry residue obtained by slow evaporation of 1,000 c.c. of mineral water.  
 22. Gas determination collected right over reservoir; a thunderstorm and dampness interfered with the test, so only emanation as absorbed in the tank could be ascertained.  
 23. Dissolved emanation driven out by heat from one liter of water (gas and tank water radio-activity

Our results compare favorably with the reports of Boltwood<sup>23</sup> from Hot Springs, Ark., and with those of Schlundt and Moore<sup>18</sup> from Yellowstone Park. Boltwood examined the waters five to six days after they had been collected and from his figures he calculates the initial radio-activity, based on the loss of activity, a radio-active solution must show after a given lapse of days. Although we have to deal with a theoretical value, which may differ from the radio-activity found immediately at the spring itself, Magnesia Spring (280 M. U.)

12. Boltwood: Am. Jour. Sc., 1905, xx, 128.

compares favorably with Boltwood's spring 70 C. (265.6 M. U.). In considering only the emanation as contained in the water, we determined quite a number of strong radio-active springs at Hot Springs, Va.; namely: Open well (156.6 M. U.; Thermalwater (112.5 M. U.); Swimming pool (109.27 M. U.); Hot Sulphur Springs (101.86 M. U.). In Hot Springs, Ark., only one other spring, 74 D., is marked with 106.8 M. U.

TABLE 6.—TESTS OF WARM SPRINGS. TEMPERATURE 97.0 F.

Time Min.	24		25		26		27		28	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	7,537.4	95.73	1,001.4	12.72	2,551.9	32.41	11,533.1	146.47	462.0	5.87
1	6,517.4	82.77	641.4	8.13	1,118.0	14.2	5,732.1	72.90	312.0	3.96
1½	5,397.4	69.55	421.4	5.35	853.0	10.83	4,747.1	60.29	202.0	2.56
2	4,297.4	54.58	371.4	4.72	793.5	10.08	5,513.6	70.02	252.0	3.20
2½	3,745.4	47.57	.....	.....	598.4	7.60	4,636.8	58.89	198.0	2.51
3	3,297.4	41.88	241.4	3.07	592.6	7.53	4,404.8	55.94	202.0	2.56
4	2,467.4	31.34	213.9	2.72	375.7	4.77	3,866.6	49.11	192.0	2.44
5	2,077.4	26.38	167.4	2.13	345.3	4.40	3,066.9	26.25	192.0	2.44
6	1,767.4	22.45	.....	.....	286.3	3.62	1,837.6	23.90	177.0	2.25
8	1,424.9	18.10	.....	.....	203.1	2.58	1,696.9	21.55	154.5	1.96
10	1,189.4	16.11	98.4	1.25	140.1	1.78	1,468.8	18.65	129.0	1.64
12	1,027.4	13.05	.....	.....	187.1	2.38	1,880.7	23.88	.....	.....
15	853.4	10.83	59.4	0.75	94.4	1.20	2,280.9	16.27	102.0	1.29
20	661.4	8.41	53.4	0.68	102.8	1.31	1,037.24	13.17	.....	.....
30	487.4	5.19	.....	.....	.....	.....	.....	.....	.....	.....

## EXPLANATION TO TABLE 6

24. Radio-activity for 1,000 c.c. per one hour carried out at the brim of the swimming-pool.

25. Collected under all precautions and taken to the laboratory at Hot Springs; examination made early next morning. Similar to the experience at Healing Springs; a considerable difference between Tests 24 and 25 will be noticed.

26. Radio-activity of gas escaping from pool in 2,020 c.c. of gas mixture and in remaining tank water (476 c.c.) tank air (values combined). The test could be continued for only 20 minutes on account of meteorological conditions; beginning thunderstorm and excessive humidity, causing discharge of leaflets.

27. Dissolved emanation obtained by boiling 1,000 c.c. of pool-water, tested in 1,900 c.c. of air and 1,000 c.c. of tank water, both values combined. Leaflets of electroscope separate only slowly; small amount of emanation in air; moist atmosphere, previous to thunderstorm; a high normal loss of ionization for the air; the results are relatively low as compared with more favorable weather conditions.

28. Radio-activity of dry sediment from 1,000 c.c. of mineral water from swimming pool.

N. B.—In the tables above the figures for the radio-activity expressed in Mache units contain only two decimals, whilst in the original computation five to six decimals are quoted.

Five springs in Hot Springs and Warm Springs and Healing Springs belong to the medium strong radio-active waters, namely: Warm Springs, 95.72 M. U.; Open Spring, 92.63 M. U.; Boiler Spring, 86.54 M. U.; Healing Springs, 69.621 M. U.; Soda Spring, 64.53 M. U.

In Hot Springs, Ark., we find three springs, namely, 63 B, 97.3 M. U.; 35 A, 65.4 M. U., and 36 A, 54.8 M. U. In Hot Springs, Va.,

two spas carry a weak emanation, that is, Clubhouse (Casino) Spring, 33.16 M. U., and Cold Spring, 31.69 M. U.

In Hot Springs, Ark., the weak springs are more numerous, namely, 30 A, 49 M. U.; 39 A, 41.6 M. U.; 69 C, 40 M. U.; 26 A, 31.9 M. U.; 66 C, 30.5 M. U.; 34 A, 29.3 M. U.; 32 A, 28.9 M. U.; 64 C and 68 C, 26.1 M. U.

TABLE 7.—TESTS OF SWIMMING-POOL AT HOT SPRINGS. TEMPERATURE 81.5 F.

Time Min.	29		30		31	
	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	8,604.2	109.27	4,654.4	59.11	3,949.8	50.16
1	7,164.2	90.98	3,274.4	41.58	3,887.8	49.40
1½	5,644.2	71.68	3,014.4	38.28	2,629.8	33.40
2	4,884.2	62.03	28,884.4	36.91	1,999.8	25.12
2½	4,212.2	53.49	2,398.4	30.56	1,813.8	23.04
3	3,784.2	40.06	2,194.4	27.87	1,589.8	12.19
4	3,099.2	39.36	1,849.4	23.49	1,249.8	15.87
5	2,568.2	32.61	1,606.4	20.30	961.8	12.31
6	2,224.2	28.25	1,364.4	17.33	859.8	10.92
8	1,794.2	22.79	1,129.4	14.34	664.8	8.44
10	1,494.2	18.98	1,048.4	13.32	445.8	5.66
12	1,294.2	16.43	914.4	11.61	379.8	4.82
15	1,140.2	14.48	842.4	10.69	297.8	3.78
20	930.2	11.81	*	.....	.....	.....
30	730.2	9.27	.....	.....	.....	.....

\* Apparatus discharged automatically (so probably the water remaining in the swimming-pool would lose in activity as shown by comparison between inflow 471,698,103.925 and outflow 189,869,380.76=281,828,272.265 Mache units through a surface of 234.6975 m<sup>2</sup>. Compared with this the swimming-pool for men at Warm Springs, corresponding to a radius of 20 feet (6 meters), and a depth of 6 feet (1.8 meters), corresponding to a cubic content 205,555.032 liters at 134 Mache units 27,544,374.288 Mache units. In that instance the outflow could not be measured on account of the inaccessibility of the outflow.

#### EXPLANATION TO TABLE 7

Probable loss in emanation per 1,000 c.c. as difference from inflow and outflow per hour, 45.9 per cent. (1 minute reading, maximal value). Measurements of swimming-pool 85.5x30.5 feet, with depth (inclined) from 3 feet 9 inches to 7 feet, or in metric square surface, 234.6975 m<sup>2</sup>. Cubic measure, 43,714.6875 cubic meters, or 43,174,687.5 liters. The maximal radio-activity would amount to 471,698,103.025 Mache units. The outflow contains as maximal value, 50.1625 Mache units.

29. Radio-activity of inflow to swimming-pool, test carried out immediately at the pool, per 1,000 c.c. and per hour.

30. Outflow per one hour and 1,000 c.c. The readings could only be made for fifteen minutes, as then the surrounding air charged with emanation, caused the leaflets of the instrument to collapse.

31. Difference between inflow and outflow per 1,000 c.c. of water and one hour, computed for fifteen minutes only, due to the cause stated above.

Three springs in Hot Springs are below 25 M. U., namely, 102° T. Spring with 15.79 M. U.; Spout Spring, 16.55 M. U., and Octagon Spring, 4.88 M. U. Thirty-two springs in Hot Springs, Ark., and all the springs recorded by Schlundt and Moore in Yellowstone Park

must be considered as very weak radio-active waters. So far as known no quantitative analyses of Saratoga Springs nor of White Sulphur Springs have been published.

The waters of Hot Springs, Va., compare favorably with European springs (Sommer<sup>24</sup>). Among the strongest radio-active springs of the world are Brambach (1,950 M. U.); Joachimsthal (Wernerlaufstollen, 600 M. U.); Lacco Ameno (Ischia, 325 M. U.); Hot Springs, Ark., 70 C. (265 M. U.), and Magnesia Springs, Hot Springs, Va. (260.9 M. U.). The Open Well at Hot Springs, Va. (156.6 M. U.) compares with Gastein Grabenbäckerquelle (155.9 M. U.), Thermalwater, Swimming Pool, Hot Sulphur Springs, Warm Springs, Open Spring, are a little lower than Landeck (Silesia) 119.8 M. U.) and higher than the spas of Carlsbad. Boiler Spring can be compared with Gastein (Chorinskiquelle, nördlich, Stollen 85.8 M. U.), Healing Springs with Gastein, Rudolphsstollen (68.8 M. U.); also Soda Spring (64.53 M. U.) with Gastein, Franz Josephs Stollen, Hinter Quelle. The Clubhouse Spring and Cold Spring of Hot Springs, Va., are a little higher than Carlsbad Mühlbrunnen, and Gastein Doctorquelle higher than Kreuznach (27.9 M. U.) and Nauheim (25.4 M. U.).

If we take into account the gas escape, the value of these mineral waters is necessarily increased, so that in bath-rooms where the atmosphere is necessarily loaded with emanation the patient must of course be benefited by such a combination. In some instances the radio-activity of the gas seems more considerable than that found in the water (Octagon Spring 102 T. Spring). The water applied in full baths owing to its radio-activity, must enforce the thermic action, and, as seen from the tables, the emanation so administered equals 4-56,000 M. U., which are doses that are usually expected from the higher radio-active European spas. If we use in our technic for the determination of the radio-activity of mineral waters the violent shaking of the water in the tank in order to free the emanation from the fluid, if, further, we know that the spraying of these waters against any obstacle also sets free the emanation, theoretically it may be presumed that half-baths, showers in any form with the mineral waters used at the bath-house set free a considerable amount of emanation, which, besides the stimulating effect on the nerves and vessels of the skin, must be inhaled by the patient. Our personal observation and experience on patients demonstrated the overstimulation of too violent procedures, which undesirable effects required several days to disappear.

Attention may be directed toward the favorable combination treatment in the pools at Warm Springs, where several millions of Mache units are contained in the water (corresponding to about 13 mg. of

24. Sommer: Emanation and Emanationstherapie, Radioaktivität d. Heilquellen.



radium), and in the swimming-pool in the bath-house at Hot Springs (with about 407 millions M. U., corresponding to about 203 mg. of radium). To the thermic action of the water is added the necessity to move, to swim, the continuous emanation escaping from the large surface of water, which the patient with his mouth close to the surface of the water must necessarily inhale. So far as could be learned, the patient seems to derive more rapid and more lasting benefit from the swimming-pool treatment. Although there seems to be present in most of the mineral waters examined a small amount of radio-active sediment, our observations emphasize the fact that the mineral waters to exert their beneficial effect must be consumed right at the spring, and that without incurring any loss of time or loss of emanation. Further, a number of observations have indicated that the air surrounding the different mineral springs contains emanation, so practically the patients are continuously exposed to such a natural emanatorium, which, during long periods of time, must contribute to the final therapeutic result.

In our study no qualitative tests were carried out to ascertain the presence of the rarer gases, helium, actinium, nor thorium emanation. From the curves, however, it would seem that the continuous and rapid fall of the leaflets of the electroscope speaks in favor of more thorium than radium emanation. For this reason it would be advisable to use the water as fresh as possible for drinking purposes. To judge from the temperature of the water and from its radio-activity, there is no relationship to be ascertained, nor would the chemical analysis allow any deductions, as to the relation between a definite amount of chemical constituents in solution and the amount of radio-active substances found.

Just as for the European spas, the high amount of radio-activity found in the spas of Carlsbad, Gastein, etc., explained to a certain extent the favorable therapeutic results in gout, chronic and subacute rheumatism and in metabolic diseases, we may infer also that for Hot Springs the high radio-activity of its waters must contribute to the favorable results observed in these diseases. The remarkable improvement in certain skin diseases observed at Hot Springs is not explained by the chemical composition only; here, too, we must attribute some effect to the radio-emanation, for the expression "eliminative effect" can only be rational if these radio-active waters are taken internally; but we have observed cures of various cutaneous disorders from the exclusive external use of the waters. With regard to the indications and contra-indications of radiotherapy in medicine, we refer to our paper.<sup>25</sup>

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25. Zueblin, E.: *The Present Status of Radioactive Therapy in Medicine*. Maryland Med. Jour., 1914, No. 5; *ibid*, 1914, No. 6.

## A STUDY OF DIFFERENT NITROGENOUS DIETS IN CHRONIC NEPHRITIS \*

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The object of this study has been to note the effect of diets containing different amounts of nitrogen on cases of chronic nephritis. To study this effect, attention has been paid especially to the different tests devised in recent years to show renal function, to the blood-pressure, and to the general condition of the patient.

Many articles have appeared in medical literature concerning the value and effects of different types of diets in chronic nephritis. No attempt will be made to review those articles which deal with the effect of diets on the general condition of the patient, nor shall we take up the literature which deals with the effect of diets in which other food elements than the nitrogen have been varied. In a study on nephritis in 1905 Widal<sup>1</sup> and Javal among other points showed that the urea of the blood became elevated in certain types of chronic nephritis when increased nitrogen in the food was consumed, or when urea was added to the diet. In 1913 Goodall<sup>2</sup> declared that the blood-pressure fell in chronic nephritis when the patients were placed on a low protein diet. In one case he found the non-protein nitrogen of the blood low after the low diet, and concluded that the general condition and blood-pressure were dependent on the presence of the end-products of protein metabolism in the blood. Seymour<sup>3</sup> in 1913, and Folin, Denis and Seymour<sup>4</sup> in 1914 reported on cases of chronic nephritis given diets containing average, high, and low amounts of protein. No accurate record was mentioned of the amount of the diet refused by the patient. They found that the patients on the high diet did not seem so well, and that the non-protein nitrogen of the blood could be increased or lowered by the diet. They found no relation between the blood-pressure and the nitrogen retention and no relation between

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1. Widal: *La Semaine méd.*, 1905, xxv, 313.

2. Goodall: *Boston Med. and Surg. Jour.*, 1913, clxviii, 761.

3. Seymour: *Boston Med. and Surg. Jour.*, 1913, clxix, 795.

4. Folin, Otto, Denis, W., and Seymour, Malcolm: *The Non-Protein Nitrogenous Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism*, *THE ARCHIVES INT. MED.*, 1914, xiii, 224.

the phenolsulphonephthalein elimination and the non-protein nitrogen of the blood when the latter was varied by the diet.

The numerous observations from which this paper is compiled were made for the most part by one or the other of us. In some instances, however, the records of the Peter Bent Brigham Hospital were used. During the time the work was in progress frequent comparisons were made between our figures and those of the hospital physicians, so that we feel no hesitancy in using their figures when it is necessary.

Any one who has worked on a problem quantitatively in a general hospital will realize the possibilities of error that readily creep in. Careful supervision of the work in these experiments makes us feel that although an occasional error may have produced some unexpected result, the figures as a whole are relatively accurate. Of course, we should not draw any conclusions from a single observation in this kind of work.

For these studies three different types of diets were selected. They all contained as nearly as possible the same number of calories and the same amount of sodium chlorid. In addition to the salt in the food enough was added in the cooking to bring the total up to approximately 4 gm. a day in each diet. One diet, called the standard nephritic diet, contained about 73 gm. of protein daily. Another, called the high protein contained about 149 gm. of protein daily, and the third, called the low protein diet, contained about 26 gm. of protein daily.

For our estimations it was assumed that if the amount of protein was divided by 6.5 the result would show the number of grams of nitrogen. Thus the high protein diet contained practically 23 gm. of nitrogen, the standard diet 11.2 gm., and the low protein about 4 gm. of nitrogen daily.

The hospital dietitian, Miss McCollough, spent considerable time in endeavoring to make up meals which contained these amounts of protein and sodium chlorid in the twenty-four hours, and which would be palatable and variable from day to day. We take pleasure in this opportunity to extend to her our thanks. The figures for values of raw food were taken from the United States government bulletin, for cooked food from Locke's<sup>5</sup> tables. In the high protein diet it was necessary to increase the caloric value from the usual 2,100 to 2,600 in order to make the meals palatable.

As many of the studies could not be carried out completely owing to the patients leaving the hospital or to other causes, we shall have to report some cases in which only certain points have been brought out. The plan followed when possible consisted in letting the patient rest for a few days after entrance to the hospital on a simple light diet.

5. Locke: Food Values, D. Appleton & Co., 1911.

After the patient had become used to the new surroundings, the standard nephritic diet was started and an accurate record kept of the amount of protein eaten at each meal. While the patient was on the standard nephritic diet, on one day 10 gm. of sodium chlorid, on another 20 gm. of urea were added to the diet, in order to study the ability of the kidneys to excrete those substances. Widal<sup>6</sup> has divided nephritis recently into those cases which are unable primarily to excrete sodium chlorid and those that are unable to excrete non-protein nitrogen. Schlayer<sup>7</sup> and Monakow<sup>8</sup> have suggested the foregoing two tests to show the kidneys' ability in regard to salt and nitrogen.

After the patient had been on the standard nephritic diet for a few days the amount of non-protein nitrogen in the blood was determined and the phenolsulphonephthalein excretion test done. The patient then was placed on the high protein diet for a few days and these two tests repeated, then on the low protein diet for a similar period and the tests were done again. The amount of fluid intake and output was recorded as was also the specific gravity of the urine. The amount of nitrogen and salt excretion during many of the experiments was studied throughout, while in others only in part. Blood-pressure observations were made from time to time.

The amount of the non-protein nitrogen in the blood and the power to excrete phenolsulphonephthalein were taken as the two most comprehensive single tests for renal function at the present time. Recent work on these tests by us<sup>9</sup> has shown that the two tests in general parallel each other, although there may be considerable variation in the phenolsulphonephthalein excretion because of passive congestion or other unknown causes, in cases in which the blood nitrogen remains constant. Our feeling is that the amount of non-protein nitrogen in the blood is slightly the more reliable test of the two. By the methods used for determinations the normal amount of non-protein nitrogen in the blood is between 20 and 30 mg. per hundred c.c. The normal excretion of phenolsulphonephthalein in two hours is more variable, but roughly from 50 to 70 per cent.

The following methods were used for making the different determinations, and references are given to the description of the technic by the originators of the tests. As no modifications were employed, we shall not give a description of the technic. For determinations of the non-protein nitrogen of the blood we used the Folin and Denis<sup>10</sup>

6. Widal: *Mouvement méd.*, 1913, i, 1.

7. Schlayer and Takayasu: *Deutsch. Arch. f. klin. Med.*, 1910-1911, cl, 333.

8. Monakow: *Deutsch. Arch. f. klin. Med.*, 1911, cii, 248.

9. Frothingham and Smillie: *THE ARCHIVES INT. MED.*, 1914, xiv, 541.

10. Folin and Denis: *Jour. Biol. Chem.*, 1912, xi, 527.

method. The method originally described by Rowntree and Geraghty<sup>11</sup> for the elimination of phenolsulphonephthalein was used. The nitrogen in the urine was determined by the method devised by Folin and Farmer,<sup>12</sup> and the sodium chlorid by the method suggested by Harvey.<sup>13</sup>

It seems most satisfactory to present the data on the individual cases in the form of tables and follow each table by a short description

TABLE 1.—DATA OF PATIENT 1078

Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
	24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
1,500	985	1.016	11.0	7.6	4.0	2.8	20.0	54	128- 80
1,350	1,200	1.012	11.2	7.5	14.0	2.5	...	..	145- 98
1,500	730	1.016	11.2	6.5	4.0	3.6	...	..	150-105
1,360	1,470	1.012	11.2	9.0	4.0	2.6	....	..	
1,375	1,040	1.016	11.2	8.3	4.0	2.4			
1,635	1,440	1.013	27.2	10.5	4.0	2.6			
1,590	1,260	1.013	11.2	8.0	4.0	2.4			
1,610	900	1.016	11.2	7.6	4.0	2.1	....	..	130- 90
					10 KCl				
1,580	1,190	1.014	11.2	8.0	14.0	3.4			
1,510	1,670	1.011	11.2	8.2	4.0	4.0			
1,505	1,440	1.013	11.2	8.6	4.0	3.4	35.2	..	
1,500	1,360	1.016	23.0	12.8	4.0	2.4	....	..	120- 80
1,500	1,640	1.018	23.0	17.7	4.0	2.1			
1,500	800	1.023	23.0	12.9	4.0	0.8			
1,500	900	1.028	23.0	15.5	4.0	1.2		..	120- 80
1,500	960	1.024	23.0	18.6	4.0	2.2	45.0	..	
1,500	1,130	1.022	23.0	20.3	4.0	3.3			
1,500	840	1.023	17.5	14.3	4.0	1.7			
1,500	940	1.025	4.0	11.6	4.0	1.2	....	..	125- 85
1,530	900	1.014	4.0	6.2	4.0	2.6			
1,130	400+	1.016	4.0	3.7+	4.0	0.9+			
1,500	1,115	1.013	4.0	6.4	4.0	2.0		48	130- 80
1,500	910	1.013	4.0	5.6	4.0	2.1	26.7	..	
1,390	835	1.013	14.0	6.1	4.0	1.9			
1,350	1,265	1.014	14.0	10.9	4.0	3.3			
1,520	1,565	1.011	14.0	12.1	4.0	3.3	....	..	125- 75
1,320	890	1.015	14.0	10.1	4.0	3.2			
1,305	990	1.020	4.0	4.6	4.0	2.8	31.2	..	

of the points of interest in that individual case, or by any comments that seemed appropriate. Following the presentation of the individual cases we shall give a summary of the cases taken as a whole to see what conclusions may be drawn.

11. Rowntree and Geraghty: Jour. Pharmacol. and Exper. Therap., 1910, i, 579.

12. Folin and Farmer: Jour. Biol. Chem., 1912, xi, 493.

13. Harvey, S. C.: The Quantitative Determination of the Chlorids in the Urine, THE ARCHIVES INT. MED., 1910, vi, 12.

The numbers used are the medical record numbers at the Peter Bent Brigham Hospital. The figures in *italic* in the nitrogen and salt columns signify the days on which the sodium chlorid and urea were added to the diet.

The first group of six cases (Tables 1-6, Chart 1) show types of nephritis which were unable to put out well added salt and urea. They fall into two groups: one in which the blood nitrogen varies with the

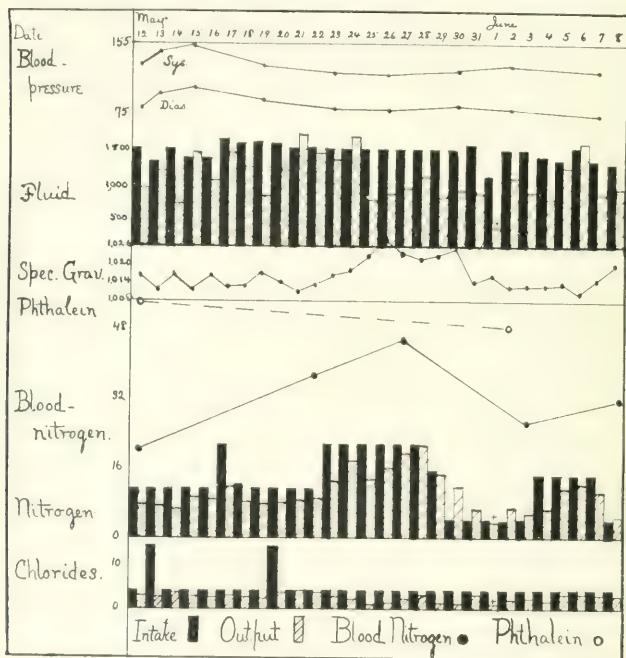


Chart 1.—Data of Patient 1078.

diet, the other in which the blood nitrogen rises despite a low protein diet.

Patient 1078 had cirrhosis of the liver with ascites in addition to a chronic nephritis. Salt and urea when added to the diet were excreted poorly. On both the standard and high protein diet the nitrogen excretion was less than the intake. The non-protein nitrogen of the blood rose steadily on both these diets and fell again on the low protein diet.



On June 4 for four successive days 20 gm. of urea were added to the low protein diet with a slight rise in the blood nitrogen. Only two phenolsulphonephthalein observations were made during this study, and they were practically the same. The blood-pressure did not show any appreciable changes with these variations in diet. On the high protein diet the patient did not feel as well as when on the other diets and had slight nausea. Ten gm. of potassium chlorid were not excreted any more readily than the sodium chlorid.

TABLE 2.—DATA OF PATIENT 624

Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
	24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
.....	.....	.....	.....	.....	10.0	8.4	.....	.....	.....
.....	.....	.....	.....	.....	10.0	10.8	.....	.....	.....
.....	.....	.....	.....	.....	10.0	11.4	.....	.....	230-125
.....	1,300	.....	11.2	11.6	14.0	8.9	.....	.....	.....
1,100	1,100	.....	11.2	11.7	4.0	6.7	.....	.....	.....
950	900	.....	11.2	11.0	4.0	5.7	25.4	45	225-124
1,300	900	.....	11.2	14.2	4.0	.....	.....	.....	.....
1,250	1,100	.....	11.2	12.7	4.0	.....	.....	.....	215-120
1,300	850	.....	23.0	18.1	4.0	.....	.....	.....	.....
1,150	1,150	.....	23.0	16.2	4.0	.....	.....	.....	.....
1,410	1,200	.....	33.0	20.1	4.0	.....	.....	.....	.....
1,350	1,450	.....	23.0	19.2	4.0	.....	.....	.....	.....
1,700	1,300	.....	23.0	18.1	4.0	.....	31.2	50	210-120
1,500	1,150	.....	23.0	Lost	4.0	.....	.....	.....	.....
1,300	1,500	1.022	23.0	23.3	4.0	.....	.....	.....	215-125
.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
950	1,300	.....	23.0	24.0	4.0	.....	.....	.....	.....
1,500	1,450	.....	11.2	11.2	4.0	.....	36.5	.....	220-120
1,300	850	1.022	11.2	13.0	4.0	.....	.....	.....	.....
1,150	1,100	.....	11.2	12.5	4.0	.....	.....	.....	.....
1,050	1,050	.....	11.2	11.0	4.0	.....	.....	.....	210-140
1,700	1,450	1.022	11.2	10.0	4.0	.....	.....	.....	.....
1,100	1,100	.....	4.0	9.0	4.0	.....	28.5	50	.....
1,600	1,000	.....	4.0	7.2	4.0	.....	.....	.....	210-130
1,650	750	1.010	4.0	5.5	4.0	.....	.....	.....	.....
1,300	1,450	.....	4.0	.....	.....	.....	21.1	54	.....

The data in this case are recorded also in Chart 1 in order to show the points more graphically.

In Case 624 accurate observations on the amount of the diet refused by the patient were not kept. Therefore we record under "intake" the amount offered. Observation in a general way made it evident that the major part of the diet was eaten. In this study the nitrogen excretion surpassed the intake on the days of standard diet and on some of the days of high protein diet. No explanation is offered for this. In this case as in the preceding one the non-protein nitrogen of the blood

rose with the high protein diet and fell with the diet poor in nitrogenous content. Also, there was no appreciable variation in the phenol-sulphonephthalein output or blood-pressure during these observations. The patient had very few subjective symptoms, and no change was noted in them during the period of study.

Patient 1197 had very few subjective symptoms from the chronic nephritis except slight dyspnea on exertion and headaches. This case showed a poor ability of the kidneys to put out salt and urea when

TABLE 3.—DATA OF PATIENT 1197

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May 16	1,175	240+	1.019	11.2	2.3+	4.0	1.0+	39.0	54	225-135
17	1,970	800	1.019	11.2	9.9	4.0	1.5			
18	1,185	855	1.019	11.2	9.1	14.0	2.0	....	..	210-130
19	1,940	1,160	1.018	11.2	13.6	4.0	3.2			
20	1,860	1,100	1.015	27.2	13.9	4.0	2.4	....	..	230-140
21	1,430	1,180	1.018	11.2	13.7	4.0	2.0			
22	1,730	1,020	1.016	11.2	10.2	4.0	1.1	....	..	215-130
23	1,865	1,015	1.016	11.2	9.0	4.0	0.6	43.1	50	
24	990	1,450	1.012	11.2	12.8	4.0	1.2	....	..	200-120
25	1,365	1,305	1.016	6.7	10.9	KCl 10 14.0	3.2			
26	1,465	950	1.016	11.2	10.6	4.0	1.4			
27	2,305	950	1.017	11.2	10.6	4.0	1.2	....	..	195-110
28	2,356	1,070	1.018	17.8	13.0	2.5	2.3			
29	1,940	1,220	1.015	19.8	13.5	3.0	2.5	....	..	178- 95
30	1,940	1,536	1.015	23.0	16.1	4.0	3.2			
31	1,850	1,275	1.017	22.5	13.1	4.0	4.1			
June 1	1,800	1,320	1.014	20.5	Lost	3.5	Lost	39.6	..	180-100
2	1,760	1,600	1.011	7.0	10.6	4.0	4.5			
3	1,640	450	1.016	4.0	4.5	4.0	1.0			
4	1,640	560+	....	4.0	Lost	4.0	Lost			
5	1,630	410+	1.010	3.6	3.0+	3.8	1.3+	25.9	..	175- 90

added to the diet. The blood nitrogen was high to begin with and remained elevated on the standard diet and the high protein diet, which were only fairly well eaten. On the low protein diet, however, the non-protein nitrogen of the blood very rapidly fell to normal. The blood-pressure in this case, with rest in the hospital and apparently irrespective of diet, fell steadily during this period of study. Only two phenolsulphonephthalein observations were made early in the study, and they showed no variation. The general condition of the patient varied very little with the change of diets, but showed a gradual improvement throughout her stay in the hospital.

Case 739, of chronic nephritis with slight subjective symptoms of hypertension, showed fair ability to put out added salt, but very little ability to put out added urea. Although the urinary nitrogen was fairly well excreted on the standard diet there was a sharp rise in the non-protein nitrogen of the blood on this diet. This was maintained but not elevated by the high protein diet, which was only fairly well eaten. On the low protein diet the blood nitrogen as in the other cases returned to normal. In this case the phenolsulphonephthalein excre-

TABLE 4.—DATA OF PATIENT 739

Date	Urine			Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pres- sure
	Fluid Intake c.c.	24-Hr. Amount c.c.	Specific Grav- ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
16	2,100	1,500	.....	.....	.....	.....	.....	22.8	58	235- 95
17	1,300	1,150	1.017	10.7	8.8	.....	.....	.....	.....	.....
18	1,650	1,150	1.016	9.1	9.6	.....	.....	.....	.....	230- 85
19	900	700	1.021	10.8	7.0	.....	.....	.....	.....	.....
20	1,250	800	1.020	10.5	.....	.....	.....	.....	.....	220- 85
21	1,000	1,290	1.012	19.1	9.8	.....	.....	41.0	32	.....
22	950	1,180	1.015	9.1	11.7	.....	.....	.....	.....	220- 85
23	1,100	580	1.019	7.6	7.3	.....	.....	.....	.....	.....
24	1,000	720	1.018	8.5	7.4	.....	.....	.....	.....	.....
25	900	500	1.020	10.7	5.0	.....	.....	.....	.....	.....
26	1,900	2,100	1.014	22.5	10.5	4.0	7.1	37.5	35	200- 90
27	1,100	900	.....	17.9	.....	4.0	4.8	.....	.....	.....
28	1,300	1,100	.....	18.0	.....	4.0	6.2	.....	.....	.....
29	1,950	1,300	.....	17.5	.....	14.0	11.2	.....	.....	230-110
30	1,750	2,100	.....	17.5	.....	4.0	9.7	36.5	52	.....
31	1,000	900	1.016	3.4	.....	4.0	5.4	.....	.....	220-100
Feb.										
1	900	500	1.019	3.2	4.0	.....	.....	.....	.....	.....
2	1,500	900	.....	3.2	.....	.....	.....	.....	.....	210- 85
3	1,300	750	.....	3.8	.....	.....	.....	.....	.....	.....
4	1,400	1,300	.....	3.1	.....	.....	.....	25.5	52	215- 80

tion fell as the blood nitrogen rose, but returned to normal before the blood nitrogen reached normal again. The blood-pressure and general condition in this case showed practically no variations with the changes in diet.

Case 762, of nephritis, entered with a moderate amount of edema and slightly broken cardiac compensation. The ability to put out added salt and urea was poor. The nephritis as shown by the non-protein nitrogen of the blood and by the phenolsulphonephthalein test was of a moderately severe grade. The diets were eaten extremely well. On a standard and high protein diet the non-protein nitrogen of the blood rose and the phenolsulphonephthalein elimination fell. The patient did

not seem in as good general condition at this time. On a low protein diet the blood nitrogen fell, but the phenolsulphonephthalein excretion remained the same. Then on a standard diet the blood nitrogen sud-

TABLE 5.—DATA OF PATIENT 762

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
20	1,600	1,300	1.015	6.0	...	10.0	...	43.4	35	190-110
21	1,550	1,500	1.022	6.0	...	4.0	3.8			
22	1,500	1,580	1.018	11.2	8.0	4.0	9.2	....	..	195-125
23	2,100	1,550	1.017	11.2	9.5	4.0	9.6			
24	1,950	1,350	1.017	11.2	9.1	4.0	8.1			
25	1,500	1,300	1.016	11.2	9.3	4.0	6.8	....	..	190-120
26	1,750	1,780	1.016	21.2	13.2	4.0	7.5			
27	1,750	1,700	1.015	11.2	10.1	4.0	7.6			
28	1,700	1,000	1.016	11.2	7.6	4.0	4.4	50.0	..	175-110
29	2,100	1,650	1.016	11.2	11.6	4.0	7.1	....	36	
30	2,100	1,500	1.017	11.2	...	4.0	6.6			
31	1,750	1,420	1.017	11.2	...	4.0	7.5	....	..	180-110
Feb.										
1	1,950	1,500	1.015	11.2	...	4.0	5.5			
2	1,900	1,500	1.015	23.0	...	14.0	6.5			
3	1,950	1,550	1.017	23.0	...	4.0	5.0	47.6	26	190-120
4	2,250	2,800	1.014	23.0	...	4.0	10.2			
5	2,300	2,050	1.019	21.5	...	4.0	6.5			
6	2,100	1,900	1.017	23.0	...	4.0	5.2	56.1	..	195-130
7	2,300	1,700	1.018	4.0	...	4.0	2.4	....	18	
8	2,100	1,900	1.014	4.0	...	4.0	5.8			
9	2,100	1,900	1.016	4.0	...	4.0	5.6	....	..	180-125
10	2,300	1,300	....	4.0	...	4.0	...			
11	1,900	1,650	....	4.0	...	4.0	...	44.7		
12	1,500	1,600	1.012	4.0	...	4.0	....	....	16	180-130
13	1,500	1,150	....	4.0	...	4.0	...			
14	1,550	1,100	1.015	4.0	...	4.0	...			
15	1,500	1,100	....	4.0	...	4.0	...	39.8	18	
16	1,500	790	....	11.2	...	4.0	...			
17	1,500	1,220	....	11.2	...	4.0	...	....	..	175-125
18	750	700	....	4.0	...	2.0	...			
19	1,500	1,100	....	11.2	...	4.0	...			
20	1,500	1,700	....	11.2	...	4.0	...			
21	1,500	1,170	1.017	11.2	...	4.0	...	78.6	15	170-120
22	1,600	1,120	....	11.2	...	4.0	...			
23	1,500	1,490	....	11.2	...	4.0	...			
24	1,500	1,700	....	11.2	...	4.0	...	....	..	150-115
Mar.								86.0	33	
7	*									

\* From Feb. 24 to March 7, diet 11.2 gm. nitrogen, 4 gm. salt each day.

denly began to rise quite markedly, and eventually the phenolsulphonephthalein excretion rose. At the same time the blood-pressure fell, and the general condition of the patient became so improved that he went home. The edema disappeared as the stored-up salt was grad-

ually eliminated. Two months later the patient reported to the out-patient department in pretty fair shape with a non-protein blood nitrogen of 46 mg. per hundred c.c. of blood. This unexpected rise on the standard diet to a higher level than formerly we cannot explain.

Case 1056 represented a severe nephritis with symptoms suggestive of pending uremia without edema. The patient did not change in condition while in the hospital and left against advice. For several days practically no diet was eaten. Added salt or urea were very poorly excreted. The phenolsulphonephthalein excretion remained only a trace throughout. The non-protein nitrogen content of the blood rose steadily even on a very low protein diet. The blood-pressure made no important fluctuations.

TABLE 6.—DATA OF PATIENT 1056

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April 2	1,500	1,200	1.014	1.3	4.1	2.0	4.0	78.9	Trace	
3	1,500	720	1.013	1.5	3.8	2.0	2.5	.....	..	210-105
4	1,900	680	1.015	1.5	5.7	2.0	2.1	.....	..	
5	1,850	820	1.015	0.6	2.2	12.0	2.9	.....	..	210-105
6	1,750	230	1.013	0.0	0.7	0.0+	0.7	.....	..	
7	1,750	410	1.015	0.0	2.1	0.0+	1.6	86.9	Trace	
8	1,700	860	1.014	0.0	3.7	0.0+	2.9	.....	..	200-100
9	1,100	435	1.012	10.0	1.8	0.0+	1.7	.....	..	
10	1,700	1,230	1.014	1.8	6.4	2.0	3.6	.....	..	180- 90
11	2,000	800	1.020	2.4	5.2	3.4	7.4	.....	..	
12	1,500	675	1.016	2.5	4.1	3.0	1.7	129.9	Trace	
13	.....	630	1.015	4.0	2.8	4.0	1.7	.....	..	210-100

The next group of five cases (Tables 7-11, Chart 2) show types of nephritis which apparently can eliminate added nitrogen in the form of urea or the nitrogen of a standard diet fairly well, but which cannot put out added salt well. The non-protein nitrogen of the blood, however, becomes elevated on the high protein diet. As in the other group it returns to normal on the low protein diet.

Patient 1097 entered the hospital in poor condition and showed auricular fibrillation and extensive edema. The edema quickly disappeared with the tremendous diuresis April 23. The non-protein nitrogen in the blood was above normal on admission. Added salt to the diet on May 1 was put out very poorly by the kidneys. Added urea was put out fairly well. The output of nitrogen in the urine the first few days was in excess of the intake, which suggested a high protein intake or retention with the edema before admission. This was con-

sistent with the high non-protein nitrogen in the blood at entrance. On the standard and low protein diet the nitrogen was excreted well and the blood nitrogen dropped to nearly normal. On the high protein diet which this patient ate well the output of nitrogen in the urine did not approximate the intake so closely. During this period of high

TABLE 7.—DATA OF PATIENT 1097

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
20	.....	.....	.....	.....	.....	.....	.....	43.4	40	190-110
21	1,300	340	1.021	4.0	5.0	1.0	0.2	....	..	215-115
22	1,000	1,865	1.016	4.0	13.2	1.0	9.0	....	..	215-120
23	800	5,800	1.013	4.0	7.9	1.0	38.0	....	..	215-120
24	800	1,200	1.018	4.0	4.8	6.0	8.6	....	..	230-130
25	1,000	1,400	1.016	6.0	7.1	6.0	4.0	....	..	230-130
26	1,000	310	1.022	6.0	5.3	6.0	1.6	....	..	230-130
27	1,000	837	1.020	6.0	8.0	6.0	2.3	....	..	210-120
28	1,300	990	1.020	6.0	7.4	6.0	2.8	....	..	210-120
29	1,200	885	1.018	6.0	6.1	6.0	3.0	....	..	210-120
30	1,200	1,030	1.019	6.1	8.5	6.0	4.0	....	..	210-120
May										
1	1,500	890	1.022	6.0	7.7	16.0	4.5	....	..	195-110
2	1,250	550+	1.018	6.0	3.5+	6.0	7.7+	....	..	195-110
3	1,500	700	1.019	6.0	4.7	6.0	5.5	....	..	180-100
4	1,200	1,465	1.017	16.0	12.5	6.0	9.6	....	..	180-100
5	1,500	410+	1.020	6.0	2.6+	6.0	3.2+	....	51	180-100
6	1,300	Lost	Lost	6.0	Lost	6.0	Lost	....	..	180-100
7	1,300	840	1.018	11.2	6.4	4.0	5.2	....	..	180-100
8	1,500	1,465	1.017	11.2	13.1	14.0	10.2	32.2	..	190-85
9	1,500	980	1.020	11.2	7.0	4.0	5.8	....	..	190-85
10	1,200	1,165	1.022	11.2	13.4	4.0	5.2	....	51	200-100
11	1,550	950	1.022	11.2	10.7	4.0	5.0	....	..	200-100
12	1,250	1,310	1.013	11.2	8.0	4.0	3.7	....	..	200-100
13	1,075	1,015	1.015	10.7	9.1	4.0	1.0	....	..	200-100
14	1,100	600+	1.020	23.0	8.1	4.0	0.6+	....	..	180-90
15	1,250	1,570	1.018	23.0	19.3	4.0	3.0	....	..	180-90
16	1,300	920	1.021	22.5	10.6	4.0	2.2	....	..	180-90
17	1,680	960	1.020	23.0	12.3	4.0	2.0	....	..	180-90
18	1,550	960	1.021	23.0	9.4	14.0	5.7	46.3	..	180-90
19	1,250	910	1.020	8.4	11.8	4.0	4.4	....	40	180-90
20	1,640	650	1.020	4.0	8.9	4.0	3.4	....	..	180-90
21	1,730	1,058	1.010	4.0	5.3	4.0	3.0	....	..	180-90
22	1,810	980	1.012	4.0	4.6	4.0	4.0	....	..	180-90
23	.....	.....	.....	.....	.....	.....	.....	37.3	..	180-90

protein diet following the standard diet the non-protein nitrogen of the blood again rose. It took apparently a larger amount of nitrogen intake to cause an increase in blood nitrogen. Again, on May 20, when the low protein diet was given, the urinary nitrogen exceeded the intake and the non-protein nitrogen of the blood fell. During the



entire period of study the phenolsulphonephthalein excretion ranged from 40 to 51 per cent. It was higher when the blood nitrogen was lower. Ten gm. of potassium chlorid added to the diet were not excreted any better than sodium chlorid.

The blood-pressure showed some variations during the stay in the hospital, but not in any special relation to the diets. It tended to be

TABLE 8.—DATA OF PATIENT 428

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Nov. 7	1,000	1,130	.....	8.0	7.0	6.0	10.3			
8	1,000	1,265	.....	8.0	8.0	6.0	11.5			
9	1,000	1,665	.....	8.0	6.3	16.0	12.3			
10	1,000	1,465	.....	8.0	6.0	6.0	10.8			
11	1,000	2,050	.....	18.0	14.0	6.0	16.8			
12	1,000	1,316	.....	8.0	...	6.0	10.0			
28	1,000	1,300	1.020	11.2	...	4.0	...	21.5	51	
29	1,000	900	.....	11.2	...	4.0	...	....	..	122- 80
30	1,000	900	.....	11.2	...	4.0	...			
Dec. 1	1,000	1,050	1.020	11.2	...	4.0	...	....	..	140- 94
2	1,000	980	.....	11.2	9.7	4.0	...	....	..	
3	1,000	840	.....	11.2	14.2	4.0	...			
4	1,000	1,450	.....	11.2	15.0	4.0	...	20.2	..	136- 90
5	1,000	1,360	.....	23.0	20.6	4.0	...			
6	1,000	1,050	.....	23.0	19.6	4.0	...			
7	1,800	1,650	.....	23.0	19.0	4.0	...			
8	1,800	1,540	.....	23.0	17.0	4.0	...	39.1	45	140- 90
9	1,800	1,600	.....	11.2	13.0	4.0	...			
10	1,800	1,200	.....	11.2	14.0	4.0	...			
11	1,800	1,300	.....	11.2	13.4	4.0	...			
12	1,800	1,150	.....	11.2	9.9	4.0	...	28.5	..	140- 94
13	1,800	1,180	1.030	11.2	10.6	4.0	...			
14	1,800	1,090	.....	11.2	11.8	4.0	...			
15	1,800	1,030	1.012	11.2	9.4	4.0	...			
16	1,800	950	.....	11.2	7.5	4.0	...			
17	1,800	980	1.020	11.2	6.7	4.0	...	23.9	45	142- 84
18	1,800	1,020	.....	4.0	7.6	4.0	...			
19	1,800	780	1.021	4.0	...	4.0	...			
20	.....	.....	.....	4.0	...	4.0	...	....	..	142- 92
21	.....	.....	.....	4.0	...	4.0	...	19.6	..	

lower the longer the patient was in the hospital, despite the period of high protein diet. On leaving the hospital the patient had no edema, his general condition was improved and the auricular fibrillation persisted.

In patient 428 the amount of food actually eaten was not measured, so the amount offered is recorded. Frequent observations, however, made us feel pretty certain that practically everything offered was

consumed. This patient showed early in November an ability to put out urea when added to the diet, but not salt. As in the preceding case it was necessary to put the patient on the high protein diet in order to elevate the non-protein nitrogen in the blood. On the low protein or standard diets the nitrogen in the blood remained normal. The phenol-

TABLE 9.—DATA OF PATIENT 1154

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May 8	2,500	2,254	1.010	11.2	13.0	4.0	10.7	30.9	45	220-140
9	1,950	1,305	1.013	11.2	9.1	4.0	5.8	....	..	
10	1,350	1,020	1.021	11.2	10.3	4.0	5.3	....	..	
11	1,500	765	1.025	11.2	6.5	14.0	2.4	....	..	260-160
12	1,450	940	1.026	9.9	10.9	4.0	3.6	....	..	
13	1,800	600	1.016	11.2	7.1	4.0	1.1	....	..	
14	2,700	3,300	1.010	20.7	19.1	4.0	4.3	....	60	255-155
15	2,100	940	1.020	9.9	9.3	4.0	1.4	....	..	230-150
16	1,900	1,830	1.017	9.7	9.3	4.0	0.9	....	..	220-150
17	2,100	1,150	1.011	8.7	7.3	KCl 10 14.0	2.7	....	..	
18	1,700	1,330	1.013	20.0	8.8	2.0	4.9	....	..	
19	1,650	1,245	1.013	22.5	12.0	4.0	2.8	35.1	..	210-140
20	1,650	1,810	1.014	20.0	13.7	2.0	4.1	....	..	
21	1,750	1,070	1.015	11.2	8.0	2.0	1.5	....	..	
22	1,670	965	1.015	8.4	7.8	2.0	1.0	....	..	205-130
23	3,100	2,980	1.005	4.0	7.0	4.0	2.0	37.3	51	
24	2,130	930	1.010	4.0	5.3	4.0	1.3	....	..	
25	1,910	1,165	1.010	4.0	5.9	4.0	3.0	....	..	180-110
26	950	740	1.011	4.0	3.7	4.0	1.2	....	..	
27	1,730	365	1.018	4.0	3.8	4.0	1.2	33.1	..	
28	1,500	650	....	4.0	...	4.0	...	....	..	190-120
29	1,700	1,100	....	6.3	...	2.0	...	....	..	
30	1,300	850	....	11.2	...	4.0	...	....	..	
31	1,900	1,150	1.012	10.7	5.7	4.0	3.0	32.6	..	170-110
June 1	1,960	1,440	1.010	10.7	6.0	4.0	2.6	....	..	
2	1,750	1,460	1.010	17.8	9.0	3.5	3.0	....	..	
3	1,800	1,150	1.014	18.6	9.2	3.6	2.6	....	..	150-100
4	1,525	1,430	1.011	19.6	9.6	4.0	2.0	....	..	
5	1,825	1,530	1.012	20.5	9.2	3.5	4.6	41.3	..	

sulphonephthalein excretion and the blood-pressure showed no appreciable variation with the changes in diet. By the time this study was made the patient was practically without symptoms except slight edema and remained so during the study.

Patient 1154 is again an example of a marked retention of added salt. In putting out his added urea it is interesting to note that it caused a diuresis as is frequently seen. He was also unable to excrete

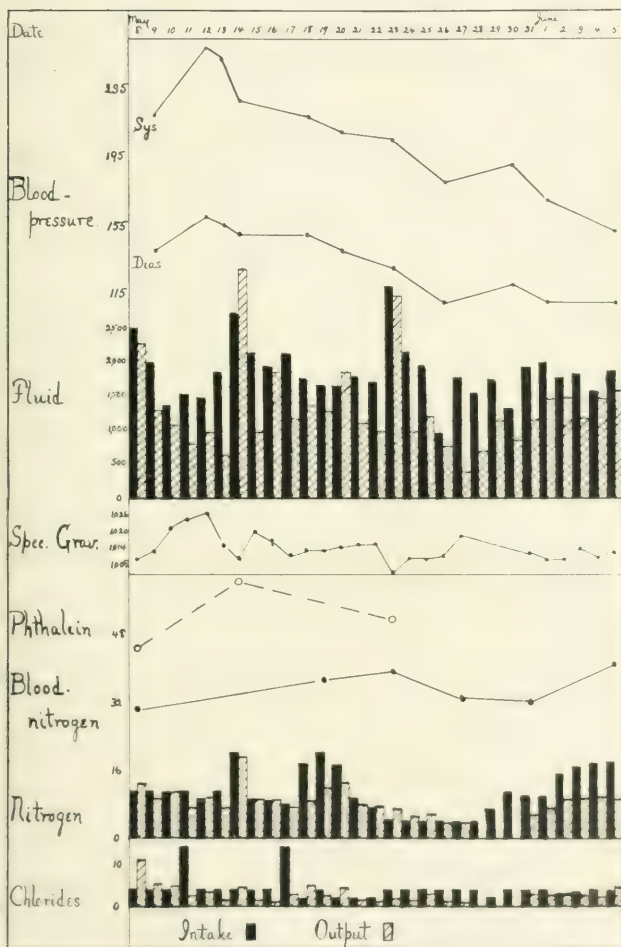


Chart 2.—Data of Patient 1154.

TABLE 10.—DATA OF PATIENT 1075

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
15	800	980	1.025	4.0	14.1	1.0	3.1	....	..	190-110
16	800	800	1.025	4.0	7.2	1.0	3.2	23.8	55	175- 95
17	800	645	1.026	4.0	10.0	1.0	3.0			
18	1,000	910	1.022	8.0+	8.6	3.0+	7.2			
19	1,000	1,100	1.020	8.0+	9.9	3.0+	10.5			
20	1,000	875	1.021	8.0+	7.5	3.0+	7.8	....	..	165- 90
21	1,550	1,280	1.016	11.2	7.0	4.0	8.8			
22	1,600	1,560	1.018	11.2	9.7	4.0	7.6			
23	1,600	2,340	1.014	11.2	10.5	4.0	10.2	....	..	165-100
24	1,700	2,740	1.012	21.2	17.8	4.0	13.0			
25	1,650	2,125	1.015	11.2	12.8	4.0	7.6			
26	1,550	1,300	1.019	11.2	7.2	4.0	8.4	20.7		
27	1,400	1,590	1.017	11.2	8.2	4.0	6.8	....	62	155-100
28	1,500	1,940	1.013	11.2	8.1	4.0	4.2			
29	1,300	1,350	1.018	23.0	18.9	4.0	3.5			
30	1,400	1,450	1.026	23.0	17.8	4.0	4.8	....	..	160- 95
May										
1	1,200	820	1.023	23.0	7.8	14.0	3.7			
2	1,700	1,340	1.025	23.0	15.8	4.0	7.7	....	..	140- 95
3	1,700	1,310	1.023	23.0	15.3	4.0	3.6			
4	1,700	940	1.021	23.0	12.4	4.0	2.0			
5	1,900	780	1.019	23.0	9.6	4.0	2.2	....	..	140- 95
6	1,700	1,665	1.018	23.0	20.0	4.0	2.0	36.5	45	

TABLE 11.—DATA OF PATIENT 817

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Feb.										
2	....	....	....	11.2	...	4.0	...	....	56	210-140
3	2,000	1,300	1.022	11.2	...	4.0	...	31.8	..	220-145
4	2,100	700	....	11.2	...	4.0	...			
5	1,700	850	....	11.2	...	4.0	...	....	..	200-130
6	1,950	750	1.023	11.2	11.6	4.0	2.4			
7	1,900	750	1.027	11.2	12.3	4.0	1.4	30.0	53	
8	1,950	850	1.023	11.2	12.0	4.0	1.0	....	..	200-135
9	2,100	1,100	1.022	20.2	18.1	4.0	1.4			
10	1,950	950	1.027	11.2	15.2	4.0	1.8			
11	1,600	950	1.027	11.2	...	14.0	4.0	....	..	195-130
12	1,500	750	1.027	23.0	...	4.0	3.6			
13	2,000	750	1.028	23.0	...	4.0	1.2			
14	1,500	950	1.026	23.0	...	4.0	3.2			
15	1,500	950	1.025	21.5	...	4.0	3.2	35.2	51	195-130
16	1,500	1,150	1.025	18.5	...	4.0	5.4			

TABLE 12.—DATA IN CASE 1200 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May 30	1,650	1,820	1.015	11.2	11.4	14.0	11.0	23.8		
31	1,460	1,700	1.016	21.2	20.2	4.0	5.6			
June 1	1,350	990	1.020	11.2	13.6	4.0	2.0			
2	1,375	925	1.024	23.0	16.0	4.0	2.0	25.3		
3	950	1,020	1.020	17.8	16.0	3.0	4.0			
4	1,425	1,230	1.018	22.0	15.4	3.8	2.7			
5	1,475	2,290	1.015	22.0	18.2	3.8	11.4			
6	1,725	1,180+	1.014	23.0	10.6+	4.0	3.6+	22.4	58	
7	1,425	760	1.025	22.0	15.2	3.8	2.0			
8	1,280	1,660	1.015	10.0	...	4.0	2.2			

TABLE 13.—DATA IN CASE 1033 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April 11	1,500	1,100	.....	11.2	.....	4.0	.....			
12	1,600	900	.....	11.2	.....	4.0	.....			
13	1,500	1,400	.....	11.2	.....	4.0	.....			
14	1,250	550	1.026	11.2	.....	4.0	.....			
15	1,300	1,150	.....	11.2	.....	4.0	.....			
16	1,500	1,150	.....	11.2	.....	4.0	...	21.6	58	
17	1,650	580	.....	11.2	.....	4.0	.....			
18	1,350	1,300	.....	11.2	.....	4.0	.....			
19	1,100	900	.....	11.2	.....	4.0	.....			
20	1,650	900	.....	11.2	.....	4.0	.....			
21	1,850	500	1.018	11.2	.....	4.0	.....			
22	1,610	900	.....	11.2	.....	4.0	...	17.6		
23	2,100	1,100	.....	23.0	.....	4.0	.....			
24	2,100	1,100	.....	23.0	.....	4.0	.....			
25	1,950	700	.....	23.0	.....	4.0	.....			
26	1,900	700	.....	23.0	.....	4.0	.....			
27	1,800	580	.....	23.0	.....	4.0	.....			
28	1,850	500	.....	23.0	.....	4.0	...	20.6		

TABLE 14.—DATA IN CASE 920 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Mar.										
26	1,500	2,300	.....	10.5	....	3.8	...	....	..	125-50
27	1,500	1,800	1.022	11.2	....	4.0	...	27.0	..	
28	1,500	1,700	.....	11.2	....	4.0	...	....	58	
29	1,500	1,450	.....	10.7	....	4.0	....	....	..	
30	1,500	950	.....	11.2	....	4.0	....	....	..	
31	1,500	1,350	.....	21.5	....	3.8	....	....	..	140-80
April										
1	1,500	1,300	.....	23.0	....	4.0	...	....	..	
2	1,500	1,150	.....	22.9	....	4.0	....	....	..	
3	1,500	1,750	.....	23.0	....	4.0	....	....	..	
4	1,500	1,580	.....	21.5	....	3.8	...	26.6	..	150-80

TABLE 15.—DATA IN CASE 1252 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
June										
18	1,400	1,100	.....	11.2	....	4.0	....	20.1	..	150-90
19	2,300	1,900	.....	11.2	....	4.0	....			
20	1,500	2,150	1.008	4.0	....	4.0	....			
21	2,260	1,660	1.008	4.0	4.0	4.0	3.2			
22	1,450	1,160	1.009	4.0	4.2	4.0	2.3			
23	2,100	200+	.....	4.0	....	4.0	...	19.2	..	



potassium chlorid any better than sodium chlorid. It was only on a high protein diet, which he ate fairly well, that the non-protein nitrogen of the blood rose, although throughout the study the blood nitrogen was on the upper border of normal limits. The phenolsulphonephthalein elimination varied a little, but not with any special change in diet. The blood-pressure showed a steady tendency to fall during the period of study, which was from the beginning of his stay in the hospital, but did not seem to bear any relation to the diets. The general condition showed slight improvement with his stay in the hospital irrespective of diet, although the albuminuric retinitis and anemia from which he suffered changed but little.

The data in this case also are recorded in Chart 2 in order to bring out the essential points more clearly.

Patient 1075 had marked edema and poor ability to excrete salt. As the salt was eliminated the edema disappeared and the blood-pressure fell steadily irrespective of the nitrogen content of the diet. The nitrogen elimination was good on the low protein and standard diets, and it was only after prolonged high protein diet, which was well taken, that the non-protein nitrogen of the blood rose. The phenolsulphonephthalein elimination fell slightly with the rise in blood nitrogen.

Case 817 is included as it shows changes similar to those in the preceding case, except that there was no edema.

The next four cases (Tables 12-15) were controls in persons, so far as we could tell, absolutely free from nephritis. Three of them were placed on a high protein diet following the standard diet, and one on a low protein after the standard diet. The diets were well taken and accurately measured. It will be readily seen that the high protein diet was taken for a considerable time without rise in the non-protein nitrogen of the blood; nor was there any appreciable drop in the patient's non-protein nitrogen of the blood after the low protein diet.

The next two cases (Tables 16 and 17) did not have the added salt and urea tests made, but seem worth recording because of the sharp rise in non-protein nitrogen of the blood, in Case 589, on a high protein diet, and in Case 785, on a diet very low in nitrogen. The latter patient died the day following the last estimation of blood nitrogen.

It would not be fair to omit the following four cases (Tables 18-21) which show varying degrees of inability to put out added salt and urea. They also show other evidences of nephritis, yet very little if any rise in non-protein nitrogen in the blood on even high protein diet. In these cases, also, there seems to be no relation between the phenolsulphonephthalein excretion or the blood-pressure and the diets. The general condition of the patients did not vary with the diets. Their symptoms

TABLE 16.—DATA OF PATIENT 589

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Dec.										
5	1,100	1,500	1.009	6.0	....	6.0	...	20.8	27	198-115
6	1,200	1,350	.....	6.0	....	6.0	...	....	..	
7	1,200	1,040	.....	6.0	....	6.0	...	....	..	
8	1,420	2,100	.....	11.2	....	4.0	....	....	..	
9	1,360	1,300	1.014	11.2	....	4.0	...	....	..	195-110
10	1,200	1,700	1.015	11.2	....	4.0	...	....	50	
11	1,200	1,500	1.018	11.2	4.2	4.0	....	....	..	
12	950	1,050	.....	11.2	5.3	4.0	....	....	..	
13	950	1,100	1.018	23.0	5.8	4.0	...	....	..	170-100
14	1,200	900	.....	23.0	8.5	4.0	....	....	..	
15	1,300	1,550	.....	23.0	12.1	4.0	...	43.5	24	

TABLE 17.—DATA OF PATIENT 785

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
June										
5	3,145	1,840	1.009	9.2	5.1	4.0	5.1	....	0	130- 90
6	2,750	1,300	1.009	10.0	3.0	4.0	3.0	117.0	0	
7	1,305	1,220	1.007	9.8	4.0	4.0	2.8	....	0	
8	2,595	460	1.007	7.0	1.5	3.5	0.64	130.0	0	
9	1,000	450	1.011	9.2	1.3	3.5	0.72	....	..	135- 95
10	2,700	380	.....	4.6	....	2.0	...	179.0	0	180- 80
11	2,500	150	.....	4.0	2.0	....	....	....	..	140- 65
12	1,300	0	.....	0.0	....	0.0	...	....	..	
13	Died									

† Convulsion.

TABLE 18.—DATA OF PATIENT 1072

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April 16	1,100	1,480	1.015	10.7	3.1	4.0	7.2	....	..	190-100
17	1,300	1,100	1.010	9.7	3.0	3.0	1.2	31.8	60	
18	950	840	1.015	10.7	6.3	14.0	4.0	....	..	200-110
19	1,300	1,180	1.009	8.8	3.5	3.0	2.7	....	..	
20	1,300	2,400	1.010	18.7	8.2	4.0	6.7	....	..	210-112
21	1,500	1,810	1.010	10.7	8.0	4.0	3.2	....	..	
22	1,680	1,915	1.010	11.1	7.4	4.0	4.0	....	..	185- 95
23	1,900	1,190	1.011	10.0	4.1	4.0	4.6	....	..	
24	1,300	2,060	1.011	12.6	3.7	4.0	2.8	29.4	..	180-100
25	1,500	1,150	1.015	17.3	7.1	3.0	1.0	....	..	
26	1,300	1,630	1.012	17.3	8.2	3.0	1.9	....	..	
27	1,500	1,320	1.011	19.0	7.5	3.0	1.2	....	..	
28	1,550	2,045	1.011	20.4	7.0	3.5	2.4	....	..	185-100
29	1,400	1,565	1.012	17.0	6.0	3.0	2.0	....	..	
30	1,500	1,570	1.013	17.0	8.4	3.0	2.5	....	..	180-100
May 1	1,350	1,630	1.012	19.7	8.1	3.0	2.0	34.0	..	
2	1,500	1,450	1.010	13.0	6.7	2.0	1.6	....	..	178-100
3	1,350	1,460	1.008	4.0	4.8	4.0	1.5	....	..	
4	1,200	1,092	1.010	4.0	4.6	4.0	1.9	....	..	170- 98
5	1,100	1,355	1.010	4.0	2.8	KCl 5 9.0	7.2	23.7	51	

TABLE 19.—DATA OF PATIENT 675

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan. 7	1,750	1,100	1.012	4.0	....	4.0	....	....	..	
8	1,780	1,150	....	4.0	....	4.0	1.9	....	..	
9	1,170	300+	....	4.0	....	4.0	3.5	34.0	54	170-105
10	1,200	700	....	4.0	....	4.0	2.3	....	..	
11	1,160	500	....	4.0	....	14.0	6.5	....	..	
12	1,100	900	....	4.0	4.1	4.0	5.2	....	..	145- 85
13	1,100	900	....	4.0	4.7	4.0	4.0	....	..	
14	1,650	900	....	8.4	4.8	3.6	...	21.6	55	
15	1,550	1,300	1.022	21.2	12.3	4.0	...	....	..	150- 90
16	1,550	1,300	1.016	11.2	9.2	4.0	...	....	..	
17	1,500	750	1.021	11.2	8.7	4.0	...	....	..	
18	1,520	880	1.011	7.9	7.4	3.0	...	26.3	..	145- 90
19	1,150	500	....	6.9	....	3.0	...	....	51	
20	800	580	....	6.8	....	3.0	...	....	..	140- 85
21	550	1,080	....	19.8	....	3.0	...	....	..	
22	1,700	1,260	1.015	13.0	8.2	2.0	...	....	..	
23	1,100	1,020	1.012	13.0	7.0	2.0	...	....	..	145- 85
24	1,550	820	1.015	13.0	6.0	2.0	...	....	..	
25	950	1,250	....	11.2	....	2.0	...	29.0	43	150- 90

TABLE 20.—DATA OF PATIENT 1029

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
12	900	570	1.021	11.0	3.1	4.0	2.8			
13	1,300	1,080	1.014	5.2	5.0	2.0	3.8	28.5	60	220-95
14	1,300	430	1.020	6.7	4.0	2.0	0.86			
15	1,500	520	1.026	2.7	6.0	12.0	3.7	....	..	185-90
16	1,300	305	1.021	4.0	1.8	2.0	2.4			
17	1,100	300	1.028	5.1	3.8	2.0	1.2	....	..	190-90
18	1,300	510	1.013	15.1	6.2	2.0	0.9			
19	1,300	605	1.015	6.7	5.5	2.0	1.3			
20	1,100	305	1.026	6.7	5.1	2.0	0.9			
21	1,300	830	1.015	15.7	5.6	2.6	1.7	19.5	75	185-95
22	1,300	1,010	1.013	9.7	6.0	1.8	3.0			180-95
23	1,500	440	1.026	10.7	5.5	2.0	2.8			
24	1,300	1,115	1.020	20.0	9.0	3.8	4.2			
25	1,300	500	1.026	12.0	7.0	2.1	1.1	....	..	185-80
26	1,300	760	1.020	14.3	8.7	2.5	2.2			
27	1,650	1,800	1.017	14.4	11.1	2.5	2.3			
28	1,600	1,270	1.020	14.0	10.8	2.5	1.1			
29	1,650	1,530	1.016	15.0	9.8	2.6	3.4	21.7		
30	1,300	1,132	1.022	15.0	11.3	2.6	2.0	....	..	205-105

TABLE 21.—DATA OF PATIENT 684

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Grav-ity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
6	950	480	....	11.2	....	4.0	...	35.9	65	210-100
7	700	690	....	11.2	....	4.0	...			
8	1,150	300	....	11.2	....	4.0	...			
9	1,250	700	....	4.0	....	4.0	5.2	....	..	200-110
10	1,900	1,300	....	4.0	....	4.0	3.0			
11	1,380	1,700	....	4.0	....	4.0	3.0			
12	2,100	1,780	....	4.0	3.2	14.0	6.2	....	..	220-130
13	1,150	910	....	4.0	4.2	4.0	7.1			
14	1,900	2,100	....	11.2	8.4	4.0	4.5	23.3	70	
15	1,900	1,700	1.015	21.1	16.0	4.0	....	....	..	210-110
16	1,380	1,950	1.014	11.2	12.6	4.0	....	....	..	
17	1,700	1,500	1.012	11.2	6.3	4.0	....	....	..	200-110
18	1,700	1,500	1.011	10.7	....	4.0	....			
19	1,650	1,900	....	10.8	....	4.0	....	27.7	57	
20	2,000	1,590	....	10.7	....	4.0	....	....	..	200-110
21	1,350	1,280	1.012	10.7	8.1	4.0	....			
22	1,300	1,100	1.019	8.2	10.8	1.5	...	....	..	180-108
23	1,650	980	1.026	21.0	17.0	3.6	....			
24	2,650	1,750	1.015	21.0	15.0	3.6	....			
25	1,650	1,620	....	21.5	....	3.8	....			
26	2,100	2,300	....	....	....	....	....	21.0	47	220-120

were slight in all the cases. In all these cases the non-protein nitrogen of the blood fell to the lower level of normal limits on the low protein diet.

In endeavoring to draw any conclusions from such a study as this or from any study of nephritis, it must be borne in mind that it is frequently impossible to decide accurately what type of nephritis from a pathological-anatomical point of view we are dealing with. In this study in most of the cases the kidneys have been studied from the point of view of their functional ability rather than with any attempt to classify the cases on an anatomical basis. The functional tests consisting in the addition of salt and urea to the diet do not permit in our series of cases such a sharp classification as Widal makes. Apparently, cases do occur in which the salt is not excreted and the nitrogen is. In the cases with a nitrogen retention, however, of our series the salt was also poorly excreted.

It is safe to say that not all of our cases of presumably the same type of functional renal disturbance act in the same way in response to the changes in diet. On the other hand, the majority of them do. Thus those cases which eliminate added urea and salt poorly tend to show an increase in the non-protein nitrogen of the blood on a diet not excessive in nitrogen, while those cases which excrete urea well but salt rather poorly, only show an increase in non-protein nitrogen of the blood on a diet rich in protein.

We find, as did Folin, Denis and Seymour, that the elimination of phenolsulphonephthalein in the urine in most of these cases of nephritis does not vary especially with the diets. In a few cases, however, it follows in a slight degree inversely to the changes in the non-protein nitrogen of the blood.

The blood-pressure did not seem to vary with the amount of nitrogen in the diet or of non-protein nitrogen in the blood as Goodall described it. It did seem to fall gradually after rest in the hospital, and especially in those cases of salt retention after the salt had been eliminated by a prolonged diet low in sodium chlorid content.

The general condition of the patient did not seem to be affected by the diets except in a few cases on the high protein diet, at which time the patients did not feel so well. This is somewhat different from Seymour's findings in which the high protein diet usually made the patients feel poorly. In his cases, however, the high protein diet was continued a longer time. The high protein diet as a rule was not enjoyed by many of the patients.

The low protein diet almost always caused a drop in the non-protein nitrogen of the blood.

Since frequently the variation in the amount of non-protein nitrogen in the blood is the only result of the changes in diet which

can be made out, the question may fairly be raised of how much value in prognosis is a rise in the non-protein nitrogen in the blood when brought about by an increased nitrogen content in the diet. Is there any appreciable change in the patient's renal condition with these changes in diet which only this test will show? These questions cannot be answered at present, but undoubtedly the diet should be considered when the amount of non-protein nitrogen in the blood is used as a basis for determining the prognosis. Presumably a rise in non-protein nitrogen in the blood in response to increased protein in the diet indicates a slighter degree of renal disturbance than is indicated by a rise when the patient is on a low protein diet.

It seems justifiable to conclude that in certain types of chronic nephritis the nitrogenous content of the diet should be carefully watched in order to prevent an increase in non-protein nitrogen in the blood. The exact effect of an increase in blood nitrogen produced by a high nitrogenous diet is not known at present, but presumably it is unfavorable to the best interests of the patient, since in some it increases their discomfort as shown by Cases 1078 and 762 of this series and cases studied by Seymour. A diet low in nitrogen content will frequently keep down to normal the non-protein nitrogen of the blood in chronic nephritis.



## METABOLISM STUDY OF A CASE OF CONGENITAL HEMOLYTIC JAUNDICE WITH SPLENOMEGALY \*

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### I. INTRODUCTION

The interesting syndrome of chronic acholuric, pleiochromic jaundice without the usual syndrome of biliary intoxication associated with anemia and splenomegaly was first noted clinically by Murchison<sup>1</sup> in 1883. Minkowski<sup>2</sup> in 1900, however, reported a very complete study of a group of cases occurring in one family. Excellent reviews of the subject, together with the literature, have been presented by Tileston and Griffin<sup>3</sup> and by Thayer and Morris,<sup>4</sup> so we shall in this paper consider only those details which have relation to the experimental work to be described.

Besides the usual hereditary form of this disease, there is a familial type and a congenital type, in which the disease dates from birth and appears in only one of the family. It may be noted from the history that the case described in this paper belongs to this type. Another type is the so-called "acquired" form, in which the disease usually appears in childhood or adolescence.<sup>5</sup>

The interesting work of Whipple and Hooper<sup>6</sup> has placed the possibility of a purely hemolytic jaundice on a firm scientific foundation. They think it possible that the endothelium of the blood-vessels is the agent which brings about the rapid change of hemoglobin to bile-pigment, and that this mechanism comes into play when there has been a destruction of many red cells with much hemoglobin free in the plasma.

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\* From the Laboratory of Dr. James P. McKelvy, Pittsburgh.

1. Murchison: *Diseases of the Liver*, Ed. 3, 1885, 481.

2. Minkowski: *Verhandl. d. Cong. f. inn. Med.*, 1900, xviii, 316; *Deutsch. Klin.*, 1905, v, 651.

3. Tileston and Griffin: *Am. Jour. Med. Sc.*, 1910, cxxxix, 847.

4. Thayer and Morris: *Bull. Johns Hopkins Hosp.*, 1911, xxii, 85.

5. Richards and Johnson: (*Jour. Am. Med. Assn.*, 1913, lxi, 1586), have reported an interesting and well-studied case of congenital hemolytic jaundice. See also Pel; *Deutsch. Arch. f. klin. Med.*, 1912, cvi, 239; Quadri; *Virchows Arch. f. path. Anat.*, 1914, ccxv, 151, and McNee, *Jour. Path. and Bacteriol.*, 1914, xviii, 325.

6. Whipple and Hooper: *Jour. Exper. Med.*, 1913, xvii, 612.

Many theories have been put forth to explain this peculiar syndrome. Pick<sup>7</sup> thought that there was present a congenital communication between the bile passages and the lymphatics. Hayem's<sup>8</sup> latest view is that it is due to syphilis. Minkowski believes that it is due to a congenital perverted function of the liver cells, and on this account, the bile is excreted into the lymphatics instead of into the bile capillaries. Chauffard's<sup>9</sup> discovery that in this syndrome there is present an increased fragility of the red cells opened up a new path for theories. The disease could be explained on this basis: that owing to the increased susceptibility of the red cells to hemolytic agents, the anemia develops and regeneration types of red cells appear in the circulation.

This increased destruction of red cells then leads to an increased formation of bile pigment and the resulting icterus. As several have failed to find hemolysins in the blood, it may be said that the increased destruction of the red cells takes place in the spleen, which leads to an increased work of the spleen and therefore accounts for the splenomegaly. This hemolytic theory is the one generally accepted to account for the symptom-complex. Troisier thinks that the fragility of the red cells depends on the fact that they have already become sensitized by union with a hemolytic amboceptor. Hutchison and Panton,<sup>10</sup> in a study of a case of the "congenital" type, think that the production of the defective red cells is a factor of considerable importance in the ultimate cause of this condition. Hawkins and Dudgeon<sup>11</sup> are also of the opinion that the primary change lies in the blood-forming organs and not in the biliary system. Widal<sup>12</sup> and his school think that the red cells are destroyed in the blood and the bile pigment is formed there. The splenomegaly then results from the increased work due to bile destruction. Banti thinks the primary lesion is in the spleen. The view of Vaquez and Aubertin has found most favor. They believe the jaundice is due to the bilirubin circulating in the blood, which is pro-

7. Pick: *Wien. klin. Wchnschr.*, 1903, xvi, 493.

8. Hayem: *Presse méd.*, 1898, vi, 121; *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1908, Series 3, xxv, 122.

9. Chauffard: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1901, Series 3, xviii, 444; *Semaine méd.*, 1907, xxvii, 25; *Presse méd.*, 1907, xv, 345; *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1907, Series 3, xxiv, 1169 and 1367; *Compt. rend. Soc. de biol.*, 1907, lxiii, 672; *Semaine méd.* 1908, xxviii, 49; *Allg. Wien. med. Ztg.*, 1908, liii, 462; *Bull. et mém. Soc. méd. d. Hôp. de Paris*, 1908, Series 3, xxv, 411; 1908, Series 3, xxvi, 94; 1909, xxvii, 293.

10. Hutchison and Panton: *Quart. Jour. Med.*, 1909, ii, 433.

11. Hawkins and Dudgeon: *Quart. Jour. Med.*, 1909, ii, 165.

12. Widal: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1902, Series 3, xix, 984; 1907, Series 3, xxiv, 1127, 1354; 1909, Series 3, xxviii, 73; 1908, Series 3, xxv, 486; *Gaz. d. hôp.*, 1907, lxxx, 1275; *Presse méd.*, 1907, xv, 641; *Compt. rend. Soc. de biol.*, 1907, lxiii, 346; 1908, lxiv, 496 and 655; 1909, lxvi, 927 and 950; *Tribune méd.*, 1907, xxxix, 711; *Arch. d. mal. du coeur*, 1908, i, 193.

duced by the liver cells as a result of attempts to change the increased amount of pigment arising from the destruction of the corpuscles. Whipple and Hooper<sup>6</sup> claim, however, that hemoglobin can be converted into bile pigments without participation of the liver. Roth<sup>13</sup> believes that hemolytic jaundice is a primary disease of the blood. Chauffard<sup>14</sup> thinks he has evidence pointing conclusively to an inherited taint, syphilis or tuberculosis, on which is added some abnormal action on the part of the spleen, as the factors responsible for congenital hemolytic jaundice.

It was thought that a complete metabolic study of this symptom-complex might throw some light on this disease. This was especially desirable on account of the fact that very little work has been done in this condition, from the metabolic standpoint. Tileston and Griffen studied the total nitrogen, urea-nitrogen, ammonia-nitrogen, creatin and creatinin in a case of chronic family jaundice for a period of three days. On a creatin- and purin-free diet, they found that the creatinin and urea values were normal, those for ammonia somewhat high. They found about 0.06 gm. of creatin in the urine per day and think the endogenous uric acid is distinctly increased. They report only one estimation of the uric acid in the complete study, however, so this result cannot be considered conclusive. They found, also, that tests for alimentary glycosuria and levulosuria were negative or inconclusive.

Minkowski<sup>15</sup> mentions that in a case of family hemolytic jaundice, Haal found an increased excretion of uric acid and a decided increase in the amount of iron in the urine.

Certain metabolic studies have been carried out in Banti's disease. It will be recalled that the name "Banti's disease" is reserved for those cases in which liver enlargement is secondary to the progressive enlargement of the spleen and associated with recurrent attacks of anemia and repeated hemorrhages from the stomach and bowels. As this disease is somewhat similar to the case described in this paper, it will be of value to review the metabolism studies carried out in Banti's disease. Umber<sup>16</sup> found a toxogenic decomposition of protein in a case of Banti's disease. He did not think it was due to the anemia present, but since the protein destruction disappeared after the removal of the spleen, he thought this destruction of the protein was due to a toxic agent produced in the spleen. This substance not only produced the anemia, but also affected the general metabolism of the organism.

In another case, with similar clinical symptoms, Umber found a retention of nitrogen and periodic variations in the excretion of the

13. Roth: *Deutsch. Arch. f. klin. Med.*, 1912, cvi, 137.

14. Chauffard: *Ann. d. méd.*, 1914, I, 1.

15. Minkowski: *Diseases of Digestive System*, edited by Billings, p. 349.

16. Cited by Umber: *Lehrbuch der Ernährung*, Berlin, 1909, p. 17.

urinary purin nitrogen. These values only slightly exceeded the upper limits for the normal excretion. The highest purin nitrogen excretion was 0.258 gm. Halpern,<sup>17</sup> in a case of splenic anemia, found that the average purin nitrogen excretion, on a purin-free diet, for a period of three days, was 0.253 gm.

## II. CLINICAL DATA

*Patient.*—M. E. H., a girl aged 11, born in U. S. A., was first seen Nov. 26, 1913.

*Family History.*—Father, mother, one brother and two sisters are all living and well. No other member of the family is afflicted in the same manner as the patient. There is no history of consanguinity, alcoholism, lues, tuberculosis or cancer.

*Previous History.*—The patient had rubella, parotitis, varicella and pertussis. No history of scarlet fever or diphtheria. Tonsillitis several years ago. No pleurisy or pneumonia. Slight attack of bronchitis this winter. Six years ago had an acute illness, with temperature 106 for a few hours. On the second day the symptoms disappeared and in one week the patient was well. At this time the enlargement of the spleen was first noted. Patient has never been strong; was treated six years ago with x-rays for a period of two weeks.

*Present Illness.*—Child has always had waxen color with a lemon tint. There has been no pruritus, no epistaxis, no dyspnea and no gastric symptoms. Bowels are regular, no diarrhea. Stools have been normal in color, but for two years after birth they were very green. The appetite is variable. No nausea or vomiting. Since her illness, six years ago, the spleen has been growing larger and the size is variable. The jaundice has been present since three or four weeks after birth.

*Chief Complaint.*—Enlargement of the spleen and persistent jaundice.

*Examination.*—General: The patient is underdeveloped and poorly nourished, weighing 63½ pounds. The skin is of a lemon yellow color, and the mucous membranes are pale. There are no eruptions. The cervical glands of the left side are slightly enlarged; submaxillary glands are enlarged; the axillary and epitrochlears are not palpable. Temperature 98, pulse 112.

Head: The nose, mouth and pharynx are normal. Tonsils large and ragged. The cranial nerves are normal, the teeth good, the thyroid not enlarged.

Eyes: The conjunctivae have a lemon yellow color. The pupils react moderately slowly to light and accommodation. Nystagmus to the left.

Chest: No deformities, no enlargement of thymus.

Lungs: Clear throughout.

Heart: Overacting. A blowing systolic murmur at the apex, over the pulmonary area, and transmitted to the left. The pulmonic second sound is accentuated.

Abdomen: Moderately distended and tympanitic. No abnormal masses, no areas of tenderness nor rigidity.

Liver: Extends from fifth space. The edge is palpable one-half inch below the costal border in the mammary line. The edge is firm and normal in outline.

Spleen: Extends forward to within one-half inch of midline and downward to the lower border of the umbilicus.

Kidneys: Not palpable.

Appendix and Colon: Negative.

Extremities: No edema or tenderness over large bones. The knee-jerks are normal.

17. Von Noorden: Metabolism and Practical Medicine, ii, 368.

Urine: Deep amber, clear, acid, specific gravity 1.021, no protein, no sugar, no bile, indican very slight. Microscopically contains a few squamous epithelial cells and a few leukocytes and erythrocytes.

Blood-Count: December 6, red blood-cells, 3,560,000; hemoglobin, 48 per cent. (Sahli N. S.); white blood-cells, 11,200; polynuclears, 78 per cent.; small lymphocytes, 14 per cent.; large lymphocytes, 3 per cent.; transitionals, 0.5 per cent.; eosinophils, 4.0 per cent.; neutrophils, 0.5 per cent. The red corpuscles show a definite variation in size, poikilocytosis present in mild degree. The red corpuscles stain uniformly well. No abnormal granulations present. One nucleated red corpuscle seen in making differential count of 200 cells. Blood platelets are present but relatively scarce. Blood-count: Feb. 14, 1914, hemoglobin, 55 Sahli (N. S.), red blood-cells, 3,740,000; white blood-cells, 12,600; polynuclears, 65 per cent.; small lymphocytes, 24 per cent.; large lymphocytes, 6 per cent.; transitionals, 2 per cent.; eosinophils, 3 per cent. Poikilocytosis, anisocytosis, variation in staining. Moderate number megalocytes, many microcytes, no nucleated reds.

Stools: Negative for blood, parasites or ova.

Wassermann reaction is negative.

### III. HEMOLYSIS TESTS OF PATIENT'S BLOOD

The work of Vaquez and Ribierre has demonstrated that in conditions of obstructive jaundice, the erythrocytes have an increased resistance to hemolysis by hypotonic salt solution. Chauffard and others,<sup>18</sup> in contrast to these results, found that the corpuscles in three cases of chronic acholuric icterus presented a greatly diminished resistance. Chauffard found that in normal individuals hemolysis started on addition of 0.44 per cent. sodium chlorid solution and was complete at 0.36 per cent.

TABLE 1.—HEMOLYSIS TESTS OF PATIENT'S BLOOD, DEC. 14, 1913\*

		Strength of NaCl Solution in Per Cent.											
		0.375	0.4	0.425	0.45	0.5	0.525	0.55	0.575	0.6	0.625	0.65	0.9
Patient's blood		+++++	+++++	+++++	++++	++++	++++	++++	++++	++++	++++	++++	0
Control normal		+	++	0	0	0	0	0	0	0	0	0	0

\* Washed cells used. In this table ++++ equals complete hemolysis; +++ equals moderate hemolysis; ++ equals slight hemolysis; + equals very slight hemolysis; 0 equals no trace of hemolysis.

In testing the osmotic resistance of the red cells of this patient, the same technic was used as that described by Richards and Johnson.<sup>5</sup> Table 1 contains the results obtained in this study, showing that the red cells of this patient had a lessened resistance toward salt solution.

18. Chauffard: *Compt. rend. Soc. de biol.*, 1902, liv, 1074. Von Stejskal: *Wien. klin. Wchnschr.*, 1909, xxii, 1701. Butler: *Quart. Jour. Med.*, 1913, vi, 145. Massaglia and Tarabina: *Gazz. d. osp. e. de clin.*, 1908, xxix, 778. Pel: *Deutsch. Arch. f. klin. Med.*, 1912, cvi, 239. Maliwa: *Deutsch. med. Wchnschr.*, 1913, xxxix, 154. Roth: *Deutsch. Arch. f. klin. Med.*, 1912, cvi, 137. Cade: *Bull. et mêm. Soc. méd. d. hôp. de Paris*, 1908, xxv, 421.

## IV. METABOLIC DATA

The patient was placed on Folin's<sup>19</sup> diet in quantities of about one-half the original amounts. It consisted of:

Whole milk, 300 c.c.; cream, 150 c.c.; malted milk, 100 gm.; sugar, 10 gm.; salt, 4 gm.; butter, 5 gm.; eggs (minus shell), about 240 gm.; water, 1,000 c.c.

This diet contains approximately 60 gm. of protein, 75 gm. of fat and 112 gm. of carbohydrate, yielding 1,395 calories or about 50 calories per kilogram body weight of the patient.

Two ounces of the above-described diet was taken out daily and the following constituents estimated: total nitrogen, phosphorus, sulphur, iron, calcium and magnesium. The fat was estimated in the five-day sample, preserving 5 c.c. of each day's mixture by means of two drops of liquor formaldehydi.

TABLE 2.—THE NITROGEN METABOLISM—

Date 1913	Vol.	Acidity in Amt. of N/10 NaOH necessary to neutralize total urine	Total Nitrogen	Urea Nitrogen		Ammonia Nitrogen		Creatinin †		
			gm.	gm.	% of total N.	gm.	% of total N.	gm.	Nitrogen	% of total N.
12/10	950	186.2	7.02	6.01	85.6	0.32	4.5	0.48	0.174	2.50
12/11	1100	294.8	8.32	7.06	84.8	0.34	4.0	0.45	0.163	1.96
12/12	975	227.6	8.35	7.04	84.3	0.35	4.1	0.36	0.131	1.57
12/13	1175	305.5	8.36	7.12	85.2	0.38	4.5	0.44	0.160	1.91
12/14	880	306.2	8.40	7.20	85.7	0.36	4.3	0.44	0.160	1.90
12/15	1050	302.4	8.10	7.18	88.6	0.32	4.0	0.42	0.152	1.88

\* Creatin was not present in the urine at any time.

A. *The Method Used in Urine Analysis.*—The nitrogen was estimated according to Kjeldahl, the total sulphur by Benedict's<sup>20</sup> method, total and ethereal sulphates by Folin's<sup>21</sup> method, the inorganic sulphates computed by subtracting the ethereal sulphates from the total sulphates and the neutral sulphur by subtracting the total sulphate sulphur from the total sulphur. The urea was estimated by Benedict's<sup>22</sup> method. The ammonia by Folin's method,<sup>23</sup> the total phosphorus by the Neumann method,<sup>24</sup> weighing the phosphorus as magnesium pyrophosphate. The iron was estimated by Neumann's<sup>25</sup> method, the total phosphates and earthy phosphates by titration with uranium acetate

19. Folin, O.: *Am. Jour. Physiol.*, 1905, xiii, 45.

20. Benedict: *Jour. Biol. Chem.*, 1909, vi, 363.

21. Folin: *Am. Jour. Physiol.*, 1905, xiii, li; *Jour. Biol. Chem.*, 1906, i, 131.

22. Benedict: *Jour. Biol. Chem.*, 1911, viii, 405.

23. Folin: *Ztschr. f. physiol. Chem.*, 1902, xxxvii, 161; *Am. Jour. Phys.*, 1903, viii, 330.

24. Neumann: *Ztschr. f. physiol. Chem.*, 1902-03, xxxvii, 129; 1904-05, xliii, 35.

25. Neumann: *Ztschr. f. physiol. Chem.*, 1903, xxxvii, 114.



solution; creatinin and creatin by Folin's methods<sup>19</sup>; uric acid by Folin's<sup>20</sup> method; calcium and magnesium by McCrudden's<sup>27</sup> method; amino-acid by Benedict and Murlin's method,<sup>28</sup> and total acidity by Folin's method.<sup>29</sup>

*B. Methods Used in the Analysis of the Food.*—The nitrogen by Kjeldahl method; total sulphur by Wolff and Osterberg<sup>30</sup> modification of Benedict's method; calcium and magnesium by McCrudden's method, after ashing and extracting the ash with hydrochloric acid; the phosphorus and iron by Neumann's method. The fat was estimated in a five-day period by Soxhlet extraction.

*C. Methods Used in Analysis of Feces.*—The feces were marked off by means of carmin into a period of five days. The nitrogen was estimated by Kjeldahl method; sulphur by oxidizing with fuming acid,

#### —AND URINARY NITROGEN PARTITION \*

Uric Acid			Amino-Acid Nitrogen		Undetermined Nitrogen		Feces Total Nitrogen		Nitrogen		
gm.	Nitro- gen	% of total N.	gm.	% of total N.	gm.	% of total N.	gm.	% of total N.	Intake gm.	Output gm.	Balance gm.
0.43	0.143	2.04	0.08	1.2	0.29	4.1	0.77	10.9	8.04	7.79	+ 0.25
0.35	0.120	1.44	0.18	2.2	0.46	5.5	0.77	9.3	8.15	9.09	— 0.94
0.41	0.137	1.64	0.15	1.8	0.54	6.5	0.77	9.2	8.25	9.12	— 0.87
0.33	0.110	1.32	0.20	2.4	0.39	4.7	0.77	9.2	8.05	9.13	— 1.08
0.49	0.143	1.70	0.17	2.0	0.37	4.4	0.77	9.2	8.25	9.17	— 0.92
0.41	0.137	1.70	0.14	1.7	0.17	2.1	0.77	9.5	8.37	8.87	— 0.50

\* Average creatinin coefficient equals 5.9 mg. of creatinin-nitrogen per kilogram of body weight.

followed by Benedict's method; phosphorus and iron by the Neumann method; calcium and magnesium by the same method as used for the food; the fat by Soxhlet extraction. Tables 2, 3 and 4 contain the results obtained in this study.

*Discussion of Table 2.*—In the period of five days, there was a loss of 4.06 gm. of nitrogen, which might be considered as evidence pointing toward a toxicogenic destruction of protein in this patient. The absorption of nitrogen is normal. The urinary nitrogen partition is normal with the exception of the uric acid, which shows a decided increase. This increase might be due to the fact that owing to the hemolysis of the erythrocytes, nucleoprotein is liberated from which the uric acid is formed and thereby an increased urinary excretion of endogenous uric acid is produced. This result speaks in favor of an increased destruction of the red cells as being a part of the condition.

26. Folin: Ztschr. f. physiol. Chem., 1901, xxxii, 552.

27. McCrudden: Jour. Biol. Chem., 1911, x, 187.

28. Benedict and Murlin: Jour. Biol. Chem., 1913, xvi, 385.

29. Folin: Am. Jour. Physiol., 1903, viii, 265.

30. Wolf and Osterberg: Biochem. Ztschr., 1910, xxix, 429.

TABLE 3.—THE SULPHUR METABOLISM AND URINARY SULPHUR PARTITION

Date 1913	Vol. c.c.	Total S. gm.	Total sulphate S.		Etheral sulphate S.		Inorganic sulphate sulphur		Neutral sulphur		Feces S. gm.	Sulphur		
			gm.	% of total S.	gm.	% of total S.	gm.	% of total S.	gm.	% of total S.		Intake gm.	Output gm.	Balance gm.
12/10	950	0.68	0.58	85.3	0.18	26.5	0.40	58.8	0.10	14.7	0.156	0.50	0.836	-- 0.336
12/11	1100	0.79	0.70	88.6	0.07	8.8	0.68	79.8	0.09	11.4	0.156	0.41	0.790	-- 0.38
12/12	975	0.74	0.64	86.5	0.14	18.9	0.50	67.6	0.10	13.5	0.156	0.54	0.896	-- 0.356
12/13	1175	0.73	0.61	83.5	0.13	17.8	0.48	65.7	0.12	16.4	0.156	0.46	0.886	-- 0.426
12/14	880	0.75	0.65	86.6	0.35	46.7	0.30	39.9	0.10	13.3	0.156	0.52	0.906	-- 0.386

*Discussion of Table 3.*—The urinary sulphur partition is normal in character, with the exception of a marked increase in the excretion of the etheral sulphates on the first and last days of the metabolism experiment. This is due, no doubt, to an increased intestinal putrefac-

TABLE 4.—THE MINERAL METABOLISM—

Date	Urine						Feces			
	CaO	MgO	Fe	Total phosphate P.		Earthy phosphate P.		Total P.	CaO	MgO
				gm.	% of total P.	gm.	% of total P.			
12/10	0.304	0.292	0.00877	0.62	91.2	0.17	24.7	0.68	0.76	0.26
12/11	0.426	0.264	0.00872	0.75	96.1	0.20	25.6	0.78	0.76	0.26
12/13	0.434	0.266	0.00874	0.66	94.3	0.12	17.1	0.70	0.76	0.26
12/14	0.640	0.254	0.00871	0.66	88.0	0.34	45.3	0.75	0.76	0.26
12/15	0.258	0.208	0.00881	0.60	92.3	0.24	36.9	0.65	0.76	0.26

tion. In the five days the patient lost 1.88 gm. of sulphur. This would be expected on account of the fact that our patient was also losing nitrogen.

*Discussion of Table 4.*—In the five-day metabolism experiment the patient lost 0.482 gm. of calcium oxid and 0.924 gm. of magnesium oxid. There was a phosphorus retention of 0.07 gm., and the amounts of total phosphates and earthy phosphates may be considered normal. There was also an iron loss of 0.1199 gm. The metabolism of iron in the case studied is of special interest on account of the relation of the spleen to the disintegration of red cells, and also on account of the increased hemolysis present in this disease.<sup>31</sup>

To interpret our results, it will be necessary to review briefly some of the more important papers that have appeared on the metabolism of iron. Lehmann, Müller, Munk, Senator and Zuntz<sup>32</sup> in 1893 published an extended study of the metabolism of the professional fasters,

31. For discussion of iron in food and its function in nutrition see Sherman: Bulletin 185, U. S. Dept. Agric., Off. Exper. Sta., 1907.

32. Lehmann, Müller, Munk, Senator and Zuntz: Arch. Path. Anat. u. Phys. (Virchow), 1893, p. 131, Supp.

Cetti and Breithaupt. During a ten-day fast, Cetti lost 7.3 mg. iron in the feces per day. Breithaupt fasted six days and lost 7.7 mg. iron in the feces per day. Stockman and Grieg<sup>33</sup> studied three normal cases and one chlorotic as regards the iron metabolism. Their results may be seen in Table 5.

TABLE 5.—IRON METABOLISM IN CASES OF STOCKMAN AND GRIEG

Experiment No.	Subject	Age	Iron in Food mg.	Iron in Feces mg.	Iron in Urine mg.	Balance mg.
1	man	20	6.2	5.07	1.27	— 0.14
2	man	35	6.2	8.10	1.23	— 3.13
3	man	20	5.6	10.87	0.67	— 5.94

## —(CALCIUM, MAGNESIUM, PHOSPHORUS AND IRON)

Feces		Balance							
Phosphorus gm.	Iron gm.	Calcium oxid		Magnesium oxid		Phosphorus		Iron	
		Intake gm.	Balance gm.	Intake gm.	Balance gm.	Intake gm.	Balance gm.	Intake gm.	Balance gm.
0.48	0.02396	0.93	— 0.134	0.32	— 0.292	1.2	+ 0.04	0.0084	— 0.0234
0.48	0.02396	0.93	— 0.256	0.38	— 0.144	1.3	+ 0.04	0.0099	— 0.0231
0.48	0.02396	1.04	— 0.154	0.36	— 0.166	1.15	— 0.03	0.0088	— 0.0239
0.48	0.02396	1.20	— 0.20	0.34	— 0.174	1.17	— 0.06	0.0084	— 0.0244
0.48	0.02396	1.28	+ 0.262	0.32	— 0.148	1.21	+ 0.08	0.0086	— 0.0242

Von Wendt<sup>34</sup> has reported six metabolism experiments, covering thirty-five days, in which the income and outgo of iron was determined. He estimates that an average mixed diet will contain from 20 to 30 mg. of iron. His results are presented in Table 6.

TABLE 6.—IRON METABOLISM IN VON WENDT'S CASES

Experiment No.	Iron in Food gm.	Iron in Feces gm.	Iron in Urine gm.	Balance gm.
1	0.100	0.008	0.001	+ 0.001
2	0.006	0.010	0.001	— 0.005
3	0.016	0.013	0.001	+ 0.002
4	0.008	0.008	0.001	— 0.001
5	0.017	0.041	0.001	— 0.025
6 (a)	0.016	0.015	0.001	0
6 (b)	0.007	0.015	0.001	— 0.009

33. Stockman and Grieg: Jour. Physiol., 1897, xxi, 55.

34. Von Wendt: Skand. Arch. Physiol., 1905, xvii, 211.

Sherman's results on the metabolism of iron are given in Table 7.

In closing, Sherman claims that the amount of iron metabolized in the body so as to be eliminated, in health is small, in fasting experiments 7 or 8 mg.; in metabolism experiments with restricted diets from 5.5 to 12.5 mg. per day, and that the amount of food-iron required for the maintenance of the equilibrium in healthy men lies between 6 and 12 mg. per day.

TABLE 7.—IRON METABOLISM

Experiment No.	Iron in Food daily	Iron in Feeces daily	Iron in Urine daily	Balance daily
1	0.0057	0.0053	0.0002	+ 0.0002
2	0.0065	0.0085	0.0002	— 0.0022
3	0.0071	0.0124	0.0002	— 0.0055

At present, since the work of Neumann<sup>35</sup> and of Neumann and Mayer,<sup>36</sup> about 1 mg. of iron, in the urine, for a period of twenty-four hours, is considered the normal output. In diseases of the blood, the following results have been obtained as regards the urinary excretion of iron. Zander<sup>37</sup> claims to have found a decided decrease in the urinary iron in chloranemia. Quinke,<sup>37</sup> however, showed that the excretion of iron was increased in the beginning of the disease, while later there was a lessened excretion. Lehmann<sup>37</sup> also found an increased excretion. Hunter<sup>38</sup> and Jolles and Winkler<sup>39</sup> have reported marked reductions in the urinary excretion of iron in chloranemia. Hunter<sup>40</sup> found a marked increase in the excretion of iron in pernicious anemia, at one time 32.26 mg. were excreted daily in the urine. Damaskin,<sup>31</sup> in pernicious anemia, reported an increased excretion, while Hopkins<sup>41</sup> found the excretion varied from traces to 8.3 mg. per day. In leukemia, an increased excretion of iron has also been found.<sup>42</sup> On comparing the results obtained as regards the iron metabolism in the study of this case of hemolytic jaundice with splenomegaly, with the results summarized above, it can readily be noted that there is a marked increase in the excretion of urinary and fecal iron, as would be

35. Neumann: *Ztschr. f. physiol. Chem.*, 1903, xxxvii, 114.

36. Neumann and Mayer: *Ztschr. f. physiol. Chem.*, 1903, xxxvii, 2 and 143.

37. Cited from Kennerknecht: *Virchow's Arch. f. path. Anat.*, 1911, ccv, 89 (contains the literature).

38. Hunter: *Brit. Med. Jour.*, 1890, ii, 1.

39. Jolles and Winkler: *Arch. f. exper. Path. u. Pharm.*, 1900, xlv, 464.

40. Hunter: *Practitioner*, 1889, xliii, 161, 321, 401.

41. Hopkins: *Guys Hosp. Reports*, 1894, vii, 373.

42. Hoffmann: *Zeit. f. anal. Chem.*, 1901, lxxiv, 40.

expected in a disease in which we have a hemolytic jaundice combined with an increased fragility of the red cells, and that the increased excretion is due to the liberation of the iron from the broken-down red cell.

TABLE 8.—THE FAT METABOLISM \*

	Date 12/10-12/14
Fat (gm.) in feces.....	18.0
Per cent. of fat in dried stool.....	26.2
Per cent. of fat intake .....	9.1
Per cent. of fat absorbed .....	90.9
Intake of fat (gm.).....	165
Per cent. of neutral fat in stool fat.....	37
Per cent. of fatty acid in stool fat.....	27
Per cent. of soaps in stool fat.....	36

\* Cholesterol not included.

*Discussion of Table 8.*—The fat metabolism is normal in character, with an absorption of 90.9 per cent. of the ingested fat. The amount of neutral fat, fatty acids and soap in the stool is normal, thereby excluding this as the cause for the loss of the calcium and magnesium

TABLE 9.—TESTS OF URINE AND FECES FOR UROBILIN, UROBILINOGEN, BILIRUBIN AND HEMOGLOBIN \*\*

Date	Urine				Feces		
	Urobilin*	Urobilinogen*	Bilirubin†	Hemoglobin‡	Urobilin‡	Bilirubin‡	Hemoglobin§
12/ 6	0	+	0	0	+	0	0
12/ 8	+	+	0	0	+	0	0
12/10	0	+	0	0	+	0	0
12/11	+	+	0	0	+	0	0
12/12	0	±	0	0	+	0	0
12/13	+	+	0	0	+	0	0
12/14	+	+	0	0	+	0	0
12/15	+	+	0	0	+	0	0
12/16	+	+	0	0	+	±	0

\* Dimethylamidobenzaldehyd and spectroscopic tests used.

† Nakayama's and Gmelin's tests used.

‡ Schmidt's test used.

§ Spectroscopic and benzidine tests.

\*\* In this table the sign + stands for present and 0 for absent.

*Discussion of Table 9.*—Although urobilin is present in the urine normally, in small quantities, its presence cannot be detected by the tests used. A positive reaction with Ehrlich aldehyd reagent or with Schlesinger's zinc acetate test usually means that there has been either an abnormal destruction of red blood-cells or an insufficiency of the liver to perform its normal function.<sup>43</sup> We think, therefore, that the marked reaction for urobilin in the feces and urine of our case may be taken as an indication of the increased hemolysis present in this condition. In the case studied by McPhedran and Orr,<sup>44</sup> they found six times as much urobilin in the feces as in the stools of a normal control. Moller<sup>45</sup> found also that the total urobilin excretion in the urine and feces is greatly increased (400 mg. in twenty-four hours). It may also be noted that blood and bile pigments were absent from the urine and feces.

#### V. SUMMARY

1. A case of congenital hemolytic jaundice with splenomegaly and increased fragility of the red cells is described together with a metabolism experiment.

2. In a metabolism experiment of five days, there was a loss of 4.06 gm. of nitrogen, while the urinary nitrogen partition is normal in character with the exception of the uric acid nitrogen, which is increased. The absorption of nitrogen was normal.

3. The urinary sulphur partition is normal in character with occasional increased excretions of ethereal sulphates. In the five days there was a loss of 1.88 gm. of sulphur.

4. In the five days there was a loss of 0.482 gm. of calcium oxid and 0.924 gm. of magnesium oxid. There was a phosphorus retention of 0.07 gm., while the amounts of earthy phosphates and total phosphates may be considered normal.

5. There was a loss of 0.1199 gm. of iron in the five days, with marked increased amounts of iron excreted in the urine and feces.

6. The fat metabolism was normal, with an absorption of about 91 per cent. of the ingested fat. The amounts of neutral fat, fatty acids and soaps in the stool were normal.

7. Urobilin and urobilinogen were present in the urine and feces. Bilirubin and hemoglobin were absent from the urine and feces.

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43. For a complete discussion of urobilin see Wilbur and Addis: Urobilin: Its Clinical Significance, *THE ARCHIVES INT. MED.*, 1914, xiii, 235.

44. McPhedran and Orr: *Canad. Med. Jour. Assn.*, 1913, iii, 14.

45. Moller: *Berl. klin. Wchnschr.*, 1908, xlv, 1639.



## FUNCTIONAL CHANGES IN EXPERIMENTAL HYDRONEPHROSIS\*

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The effects of back-pressure on the kidney have been studied by a number of investigators in the clinical, physiological and pathological fields. The records of experimental and clinical cases show that with partial or complete occlusion of the ureter hydronephrosis almost invariably results. Instances in which atrophy has occurred have been reported, but a careful study of the records reveals but few in which there was a true, primary atrophy—that is, one that was not preceded by a temporary hydronephrosis. A thorough review of the literature on this point has recently been presented by Scott.<sup>1</sup> Kawasoye,<sup>2</sup> in a publication that appeared at about the same time, discusses at length the difficulty of producing complete atresia of the ureter. His own method consisted in tightly knotting the ureter and ligating the free end. In ten rabbits so treated, the histological evidences of hydronephrosis were found in every instance, the duration varying from two to seventy days.

As regards the physiological effects of back-pressure on the kidneys, the work of previous investigators is here reviewed, because the experimental studies presented in this article are essentially functional. Their methods of procedure can be grouped into two classes, fundamentally different one from the other. In the first group the methods, in general, consisted in establishing a constant pressure in one ureter and comparing the secretory ability of this kidney with that on the opposite side. The determinations were not preceded by any prolonged back-pressure, and consequently the results represent simply the ability of a normal kidney to secrete against an increased pressure. In the second group one ureter was ligated, and after a varying length of time the obstruction was released and the functional capacity of the two sides compared. The latter methods give rise to conditions that approach more nearly a true pathological picture, for

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1. Scott, G. D.: Experimental Hydronephrosis, Surg., Gynec. and Obst., 1912, xv, 296.

2. Kawasoye, M.: Experimentelle Studien zum künstlichen Ureterverschluss, Ztschr. f. Gynäk., Urol., 1911-1912, iii, 172.

the results represent the functional derangement following the damage to the kidney by prolonged intrapelvic pressure.

*First Group.*—Hermann,<sup>3</sup> working in Ludwig's laboratory, in 1859, found that an intra-ureteral pressure of less than 50 mm. of mercury resulted in a diminution in the flow of urine and in the secretion of urinary solids. A pressure above 50 mm. of mercury caused a complete suppression. Lépine and Porteret,<sup>4</sup> experimenting on dogs, found that with intra-ureteral pressures of from 20 to 45 cm. of water, the secretion of water and chlorids was diminished. They note the interesting fact that when the pressure was low the diminution in the amount of urea was relatively more marked than that of the water and chlorids, while with higher pressures the water and chlorids were more diminished than the urea. Lindemann,<sup>5</sup> working on dogs, found that with a pressure in one ureter of from 10 to 43 cm. of water, the amount of urine and urea was lessened, as compared with the other side, while the sodium chlorid remained unchanged. With a pressure below 50 mm. of mercury the blood-flow through the kidney was unaffected, but with one of from 50 to 210 mm. the flow was retarded. Schwartz<sup>6</sup> reported in 1902 that the kidney (in dogs) under a back-pressure of from 10 to 25 cm. of water secreted more urine, but of a lower specific gravity; although the concentration of urea, nitrogen and sodium chlorid was less, the absolute output of these substances was greater on account of the increased volume of urine. After the injection of phloridzin, reducing bodies were more marked in the urine from the pressure side. Methylene blue appeared simultaneously from both ureters. Under the influence of diuretics, sodium chlorid or sodium iodid, the amount of urine which flowed from the affected side was double that from the other, the percentage of chlorids and iodids less, while the absolute amount was greater. If the pressure was maintained beyond the usual time (from seventy-five to 150 minutes) or if it was raised, diuresis stopped. Working on rabbits he found that a pressure of from 2 to 3 cm. of water stopped the secretion. Cushny<sup>7</sup> worked on rabbits and

3. Hermann, M., quoted from Cohnheim: *Lectures on General Pathology*, translation by A. B. McKee, London, 1890, p. 1223; *Back Pressure on the Ureter and Its Effects on Urinary Flow*, *Sitzungsberichte der Wiener Akademie*, xxxvi, 1859.

4. Lépine and Porteret: *Sur la composition de l'urine sécrétée pendant la durée d'une contre pression exercée sur les voies urinaires*, *Compt. rend. Acad. d. Sc.*, 1888, cvii, 74.

5. Lindemann, W.: *Ueber die Wirkung der Gegenruckerhöhung auf die Harnsecretion*, *Z. path. Anat. u. allg. Path.*, 1897, xxi, 500.

6. Schwartz, Leo: *Ueber Harnveränderung nach Ureterbelastung*, *Zentralbl. f. Physiol.*, 1902, xvi, 281.

7. Cushny, A. R.: *On Saline Diuresis*, *Jour. Physiol.*, 1902, xxviii, 431.

found that with a pressure of 30 mm. of mercury, after the intravenous injection of sodium chlorid and sodium sulphate, the volume of urine and the concentration of the chlorids and sulphates was less from the affected side. Later the same investigator reported<sup>8</sup> a repetition of these experiments on dogs, with the same findings. Filehne and Ruschhaupt<sup>9</sup> found that in rabbits a pressure in one ureter of from 7 to 27 cm. of water caused uniformly a diminution in the amount of urine from that side, diuretics having been injected. On release of pressure there followed a greater urinary flow from the affected side than from the normal one. Brodie and Cullis,<sup>10</sup> working on decerebrated dogs, found that a back-pressure of from 10 to 20 cm. of water in one ureter caused an increased flow of urine and an increased elimination of sulphates during the diuresis caused by the injection of sodium sulphate. This effect is most marked at 10 cm. of water, and they placed the limits of increased secretion at from 10 to 20 cm. They confirm the observation of Schwartz that the excretion of reducing bodies, following the injection of phloridzin, is greater from the pressure side.

*Second Group.*—Heidenhain<sup>11</sup> tied one ureter (in rabbits), and after twenty-four hours injected indigocarmin. As soon as the dye appeared in the urine from the normal side, the animal was killed and the deposition of the indigocarmin in the two kidneys was studied grossly and microscopically. He notes that in all cases the ureter was distended above the ligature and the kidney on that side was edematous. The blue dye was evident, grossly, in both kidneys but was distinctly less in the affected one. Microscopic examination showed that while clumps of the carmin were lying in the lumen of the tubules, yet the blue granules were not present in the tubular cells as in the normal kidney. Lindemann<sup>12</sup> ligated the ureter on one side, and after an hour and a half studied the excretion of indigocarmin from the two kidneys. He found that there was a diminution in the amount of the dye excreted by the affected side. Pfaundler<sup>13</sup> tied the ureter

8. Cushny, A. R.: Acid Secretion by the Kidney, *Jour. Physiol.*, 1904, xxxi, 188.

9. Filehne and Ruschhaupt: Die Diurese bei AbflusserSchwerung, *Arch. f. Physiol.*, 1903, xcv, 409.

10. Brodie, T. G., and Cullis, W. C.: On the Secretion of Urine, *Jour. Physiol.*, 1906, xxxiv, 224.

11. Heidenhain, R.: Versuche ueber den Vorgang der Harnabsonderung, *Arch. f. Physiol.*, 1874, ix, 10.

12. Lindemann, W.: Ueber Veränderungen der Nieren infolge von Ureterunterbindung, *Ztschr. f. klin. Med.*, 1898, xxxiv, 299.

13. Pfaundler: Ueber die durch Stauung im Ureter zu Stande kommende Veränderung der Harnsecretion, *Beitr. z. Chem. Phys. u. Path. (Hofmeister's)*, 1902, No. 2, p. 330.

on one side (in dogs), and after varying intervals of time (from fifteen minutes to six hours), collected the fluid which had accumulated behind the ligature and compared it with that secreted by the other kidney during the same period. He found that the volume of urine was greater, but that the concentration of urea and sodium chlorid was less. Bainbridge<sup>14</sup> ligated one ureter (in cats) and after varying intervals of time anesthetized the animal, measured the pressure in the ureter and tested the fluid that had accumulated back of the obstruction. He then emptied the pelvis, effected diuresis by the injection of salt, and collected the urine from the sound and the hydro-nephrotic kidney. He found that the secretory power of the affected kidney, as evidenced by the amount of water and solids collected, steadily diminished from day to day but was not entirely lost at the end of two months. If tested within a few days the damaged kidney sometimes secreted more water, but the nitrogen total was always low. The ability to excrete acids, also, was impaired. Kawasoye<sup>2</sup> tied off one ureter in each of nine rabbits, killing them at intervals varying from a few hours to a month; in each case indigocarmin was injected twenty minutes before death. Histological examination showed that the dye was present in the tubular epithelial cells in decreasing amounts up to twenty-four hours, and after forty-eight hours none was seen. In another series of seven rabbits the obstruction was relieved at varying intervals of time, and it was found that complete restoration of functional ability, as shown by indigocarmin as a test, took place after four days, incomplete restoration after from seven to fourteen days, and after twenty-one days no dye at all was secreted. Steyrer<sup>15</sup> reports two clinical cases in which a partial atresia of one ureter was caused by a unilateral ureterovaginal fistula. The urine was collected from the two sides simultaneously and studied. He observed that in both cases the urine from the affected side was increased in amount but of a lower specific gravity and molecular concentration than that from the normal side.

As a result of the work of these investigators it is quite clear that increased back-pressure on the kidney will cause definite functional changes. The amount of urine secreted apparently varies with the degree of intra-ureteral pressure, there being, with low pressures, an increased flow, while with higher pressures, the flow is diminished. With but one exception (Brodie and Cullis) there is reported a decrease in the concentration of solid constituents. The excretion of indigocarmin is materially reduced, as agreed by all.

14. Bainbridge, F. A.: The Effects of Ligature of One Ureter, *Jour. Path. and Bacteriol.*, 1906, xi, 421.

15. Steyrer, Anton: Ueber Osmotische Analyse des Harns, *Beitr. z. chem. Phys. u. Path.* Hofmeister's, 1902, No. 2, 312.

The effects produced by back-pressure, extending over a longer period of time than the foregoing experiments—conditions more nearly approaching that met clinically, have not been previously undertaken. For this reason we present a study of the functional changes that occur from day to day in an animal when the only deviation from normal is an increased intra-ureteral pressure.

#### METHOD OF PROCEDURE

In order to study the effects of increased back-pressure on the kidney in the living animal, over an extended period of time, three procedures are open: first, to obstruct the urethra; second, to produce a partial occlusion of both ureters, or, third, to produce an obstruction in one ureter, with removal of the kidney on the other side. The latter method was considered to be the most reliable, in that evidences of functional changes could be definitely attributed to the involvement of the one kidney. Before adopting it, however, a unilateral nephrectomy was performed in two dogs and the functional tests carried out several times during the succeeding two weeks. No change from the normal was found.

Several devices for producing a partial obstruction of the ureter were then tried. Rigid bands, sections of silk urethral catheters, were at first used, being placed about the ureter and held in position by silk sutures. This method proved to be unsatisfactory, in that it entailed stripping a short length of the ureter, resulting in a localized edema and marked narrowing.

Elastic bands were next employed, the use of which was suggested by Scott's work,<sup>1</sup> and a preliminary trial on the ureter of a dog which had just been killed, gave promise of success. The kidneys, ureters and bladder were dissected free, placed in their normal relations in warm, physiological saline solution, and the experiment conducted as follows: A rubber band, 1.5 mm. in width and 1 mm. in thickness, was placed about the ureter, from 3 to 4 cm. above its entrance into the bladder, the ends of the elastic being held together by silk suture. The bladder was laid open so that the ureteral orifice was plainly visible at the trigone. A cannula was inserted into the ureter above the obstruction. To this cannula was attached a water manometer, the fluid, normal saline, being colored by an indicator, and the pressure determined at which the fluid escaped past the obstruction. When the elastic band was tightly fixed about the ureter, but without tension, it was found that a water pressure of 100 cm. was necessary before the fluid passed the obstruction; whereas when the elastic band was more loosely placed—that is, when a definite clear space could be seen between the ureteral wall and the point where the silk ligature held the

ends of the rubber band—the ureter became permeable at a pressure of from 20 to 30 cm. of water. In light of the results of previous investigators we considered this to be the pressure most likely to produce the desired effects.

This method was then applied to the living animal, as follows:

Doc 15.—A small, black, male dog, weighing 5.5 kg., was operated on in the following manner: The abdominal wall was shaved and the skin cleaned in the usual way. Rigid, aseptic surgical technic was employed throughout. Under ether anesthesia the abdomen was opened in the median line, the intestine packed off, the left kidney decapsulated, and the stalk containing the renal artery, vein and ureter was ligated and sectioned. Following left nephrectomy, the right ureter was palpated just above its entrance into the bladder wall and a rubber band was passed around it and tied as described above.<sup>16</sup> The abdominal wall was closed in three layers with continuous silk sutures. As it was impossible to catheterize such a small male animal no functional studies were performed in the next week, the urine only being examined in the routine manner for albumin and casts. The animal passed at least an average daily amount of urine and appeared to be in good health. The full allowance of meat and water was taken and there was no loss of weight. One week after the operation the dog was killed, and a definite enlargement of the right ureter above the band, with a moderate hydronephrosis and enlargement of the right kidney was found. The capsular veins were enlarged and very prominent. Otherwise the necropsy revealed nothing abnormal, there being no evidence of infection in the urinary tract or elsewhere in the body.

The pressure of water necessary to overcome the obstruction was then determined in the manner previously described. This pressure was found to be 30 cm. of water. Histologically, the right kidney showed marked and uniform dilatation of the tubules of the pyramids. The convoluted tubules were but slightly dilated and their epithelium was columnar. Few casts were seen. The glomeruli showed no change. The walls of the larger blood-vessels were thickened.

The method proving satisfactory, we proceeded to apply it to female dogs and study the renal function before and after operation. In only one of the seven submitted to this procedure did the method fail to produce the desired effect. In this instance, Dog 13, the elastic band was placed too tightly about the ureter, and although the animal passed between 100 and 200 c.c. of urine in forty-eight hours, anuria then developed, followed by the typical course of complete renal insufficiency as observed in dogs. The pressure necessary to overcome the obstruction, determined at necropsy, amounted to 70 cm. of water, much above that determined at the necropsies of the remaining six animals. There was moderate distention of the ureter above the obstruction with definite dilatation of the pelvis of the kidney. The whole organ was larger than the one previously removed from the other side. The capsular veins were engorged.

Histological Examination: The glomerular capsules were dilated and the tufts did not fill the capsular space. The tubules in general were slightly dilated, although this was not so marked as the glomerular change. The tubules were filled with amorphous, pink material which suggested forming casts. The epithelium of the tubules was swollen and watery, the differentiation between the epithelium and masses of exudate being very poor. The interstitial tissue was less conspicuous than normal.

16. More accurate methods of estimating this pressure at operation are being considered.



## METHODS USED IN THE FUNCTIONAL STUDIES

The dogs were kept in metabolism cages, given a constant diet, 200 gm. of ground beef, and allowed to drink as much water as they desired. The beef was frequently analyzed for the total nitrogen content. It is to be emphasized that only in one or two instances was water forced. A twenty-four-hour specimen of urine was collected, the dog being catheterized at the beginning and end of this period. When the phenolsulphonephthalein or other tests were performed, a portion of the urine collected by catheter was added to the total collection. It was observed in the first experiment that one of the most striking features was the accumulation of incoagulable nitrogen in the blood. Consequently, a nitrogen partition of the twenty-four-hour specimen of the urine was determined daily in conjunction with the frequent estimation of the incoagulable nitrogen in the blood. The total nitrogen in the urine was determined by the usual Kjeldahl-Gunning method, the urea by the method described by Marshall<sup>17</sup> and the ammonia nitrogen by Folin's aeration method. The urea and ammonia determinations were sometimes omitted because of putrefactive changes occurring in the urine in spite of the constant use of toluene. The urine was tested periodically for reducing substances with Fehling's solution and for albumin with the heat and acetic acid, and Heller's test. The urinary sediment was also examined at the same time for casts, cells, etc.

The phenolsulphonephthalein test of Rowntree and Geraghty was employed according to their original technic.<sup>18</sup> The urine was collected at the end of one or two hours, by catheter, and the percentage of the dye excreted determined colorimetrically. It is recognized that the residual urine lying behind the obstruction should have a tendency to decrease the absolute amounts of phenolsulphonephthalein recovered within a definite time after injection. To eliminate this factor as much as possible, water was forced as a routine, insuring free diuresis and rapid passage of urine into the bladder. This does not entirely correct the error, but it remains a constant one, and changes in the amounts of phenolsulphonephthalein and lactose recovered from the bladder indicate corresponding changes in the amounts excreted by the kidney.

The lactose test was carried out according to the method described by Schlayer,<sup>19</sup> 2 gm. being injected intravenously.

The phloridzin test, advocated of late years by Roth,<sup>20</sup> was used in the course of the experiments, 5 mg. being injected intramuscularly according to his technic.

The incoagulable nitrogen and urea content of the blood was determined at frequent intervals. The blood was taken according to the method used by Folin and Denis,<sup>21</sup> specimens being drawn into 5 c.c. pipets. One specimen of 5 c.c. for the estimation of incoagulable nitrogen was placed in a 50 c.c. measuring flask and 95 per cent. alcohol added up to the mark. The second specimen of 5 c.c. was run into a test-tube containing 1 c.c. of a 1 per cent. sodium oxalate solution; the urea content of this specimen was determined at

17. Marshall, E. K.: A Rapid Clinical Method for the Estimation of Urea in the Urine, *Jour. Biol. Chem.*, 1913, xiv, 283.

18. Rowntree, L. G., and Geraghty, J. T.: The Phthalein Test, *THE ARCHIVES INT. MED.*, March, 1912, p. 284.

19. Schlayer and Takayasu: Untersuchungen über die Function kranker Nieren, *Deutsch. Arch. f. klin. Med.*, 1910, xcviii, 17.

20. Roth, Max: Welchen Wert hat die Phloridzinmethode für die Functionelle Nierendiagnostic? *Verhandl. d. deutsch. Gesellsch. f. Urol.*, Third Kongress, 1911, p. 192.

21. Folin, Otto, and Denis, W.: New Methods for the Determination of Non-Protein Nitrogen, Urea and Ammonia in Blood, *Jour. Biol. Chem.*, 1912, xi, 527.

once according to Marshall's method.<sup>22</sup> This procedure being carried out so soon after withdrawal, the ammonia content of the blood could be neglected. After leaving the first specimen in 95 per cent. alcohol for at least twenty-four hours, the nitrogen content of the filtrate was determined, using the micro-method of Folin and Denis.<sup>23</sup> Their method was slightly modified in that to recover the ammonia after digestion, combined distillation and aeration was used instead of an air current.<sup>23</sup>

The depression of the freezing point in the blood-serum was determined with the Beckmann apparatus.

The histological technic was as follows: The tissues recovered at necropsy were fixed in 4 per cent. solution of formaldehyd. Sections were cut from paraffin blocks and stained in hematoxylin and eosin.

The following condensed protocol is given as illustrative of the usual course that followed ureteral obstruction. For the daily routine examination of the blood and urine, see Table 8.

Doc 19.—Black and white female, fox terrier, weight 7.75 kg. May 22, 1914: Urine shows nothing abnormal on routine clinical examination. Phenolsulphonephthalein, 88 per cent. in two hours. Lactose normally excreted in four hours. Total nitrogen in urine for past three days averaged 6.88 gm.

May 25, 9 a. m.: Blood analysis: Total incoagulable nitrogen 27 mg. and urea nitrogen 13 mg. per hundred c.c. of blood. 3 p. m.: Under ether anesthesia, left nephrectomy with placing of elastic band about right ureter 3 cm. above the bladder. General condition following the operation excellent.

May 30: The dog has made an excellent and rapid recovery from the operation five days ago. The wound has healed by first intention. The full allowance of food and water has been taken daily, and objectively the dog is perfectly normal. The phenolsulphonephthalein excretion has steadily diminished until to-day it is 35 per cent. in two hours; the blood nitrogen likewise increased until it now stands at 102 mg. per hundred c.c.; the urea nitrogen is 69 mg. per hundred c.c., being a well-marked increase in its percentage of the total nitrogen. The average daily output of urine has about doubled that recorded before operation. The daily excretion of nitrogen in the urine has remained practically the same, averaging 6.27 gm. in twenty-four hours.

June 5: For the past four days the dog has not taken its allowance of meat, but has drunk the full 300 c.c. of water. This is the only symptom of any possible general disturbance, the animal being quite lively. Lactose delayed until eight hours. Phenolsulphonephthalein excretion shows little change (30 per cent. in two hours). The incoagulable nitrogen in the blood has dropped to 76 mg. per hundred c.c. The dog has lost 450 gm. in weight since May 30, 1914. For the past two days the polyuria has almost ceased. The daily output of nitrogen in the urine has dropped to 3.58 gm. This corresponds fairly accurately to the lessened intake of nitrogen.

June 8: Weight, 7.15 kg. Nitrogen in blood has increased to 96 mg. per hundred c.c. Phenolsulphonephthalein excretion 25 per cent. in two hours; urine 260 c.c. in twenty-four hours, trace of albumin, no casts. Total nitrogen in urine has remained low, averaging 3.3 gm. despite the fact that the food intake has been practically normal for several days.

June 9: During the past twenty-four hours the dog passed but 90 c.c. of urine and has eaten only 30 gm. of meat. Despite the small volume of urine the specific gravity and the concentration of nitrogen is lower than that of the day before.

22. Marshall, E. K.: A New Method for the Determination of Urea in Blood, *Jour. Biol. Chem.*, 1913, xv, 487. Van Slyke, D. D.: A Method for Quantitative Determination of Aliphatic Amino Groups, *Jour. Biol. Chem.*, 1911, ix, 185.

23. This method was devised by B. B. Turner and has been used in this laboratory for several months, and has proved very satisfactory. It will be published later.

June 12: The dog jumps about and is lively, but examination reveals early signs of distemper. Temperature 38 C. (100.4 F.), pulse 140. Lactose delayed until ten hours. Phenolsulphonephthalein, 16 per cent. in two hours. Blood (60 c.c.) withdrawn for nitrogen partition. This shows: total incoagulable nitrogen, 92 mg.; urea nitrogen, 53 mg.; amino-acid nitrogen,<sup>22</sup> 4 mg. per hundred c.c. Freezing point of serum, 0.59. Total twenty-four-hour urine output, 260 c.c., nitrogen in urine, 2 gm.

June 13, 1914: Dog killed by chloroform. Necropsy: Thorax shows no abnormality. Lungs and heart clear. Abdomen: No signs of infection about scar, peritoneum everywhere clean and glistening. No free fluid; all abdominal viscera appear normal except the right kidney and ureter. No scar tissue or signs of infection at the site of left nephrectomy. At the site of the rubber band is a fair amount of rather dense scar tissue. Above this point the ureter is thin walled, and markedly dilated; below it is normal in size and appearance.

The relation between the increased incoagulable nitrogen in the blood and the phenolsulphonephthalein excretion during the first few days of the experiment is well seen in Figure 1.

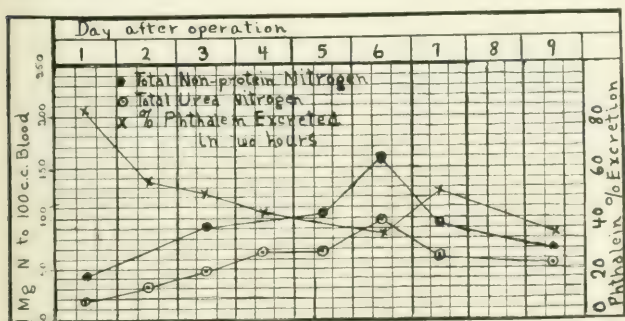


Fig. 1.—Relation between the increased incoagulable nitrogen in the blood and the phenolsulphonephthalein output during the first few days of the experiment with Dog 19.

#### COMMENT

The clinical course which followed the placing of a band about the ureter can be divided into two stages. During the first period the animals were objectively normal, the only evidences of derangement being a mild polyurea, a well-marked thirst, and the cumulative phenomena in the blood. The common symptoms of toxemia, such as loss of appetite, vomiting or diarrhea, appeared but rarely, the dogs being bright and lively. Indeed, two of them, Dogs 10 and 19, were almost abnormally so. The thirst was at all times present and was undoubtedly secondary to the polyuria, for the urinary output frequently exceeded the fluid intake over a period of several days at a time, as an examination of the tables will show. There was never any evidence of edema, but there was, in all cases, a steady, gradual loss

of weight. Determination of the number of red blood-cells and hemoglobin in Dogs 16 and 17 showed that there was no anemia. The second stage of the clinical course was the toxic period that preceded death, and it was of short duration, the longest being seven days. The characteristic features of the intoxication were loss of appetite, vomiting, progressive weakness, and the frequent passage of fluid stools containing mucus and traces of blood. There was definite slight trembling and muscular twitching. No convulsions were observed, but as most of the dogs died during the night, convulsions may have occasionally immediately preceded death. Drowsiness or

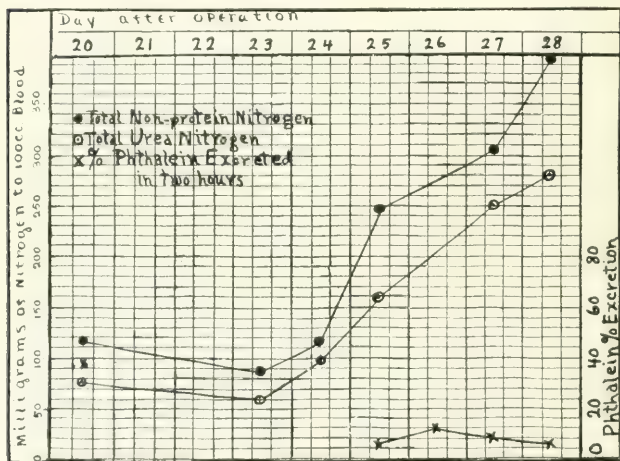


Fig. 2.—Relation between the increased incoagulable nitrogen in the blood and the phenolsulphonephthalein output a few days before death. Dog 10.

coma was certainly not present. Although very weak, the animals remained awake and seemed mentally alert. One animal was observed constantly for several hours before death, and utter weakness without dyspnea or irritative phenomena characterized the final picture. The respirations became gradually shallower and the pulse weaker until death occurred.

In brief, it seems that the establishment of a moderate back-pressure on the kidney had at first very little effect on the general condition of the dogs. There were, however, cumulative phenomena in the blood and changes demonstrable by functional tests, together with a mild polyurea. After a varying length of time there was a sudden

change, and a severe and rapidly fatal intoxication set in. During this period the functional tests indicated very marked renal insufficiency; examination of the urine together with the necropsy findings showed that pyelonephritis was present in every case.

The determination of the amounts of incoagulable nitrogen in the blood revealed striking changes. There was an immediate, sharp initial rise in the total incoagulable nitrogen, with a relatively greater increase in the urea nitrogen content. This urea nitrogen sometimes amounted to as much as 90 per cent. of the total. In general, following the first sharp rise, the nitrogen maintained a fairly constant level with but moderate fluctuations. This continued to within a few days of death, when, coincident with the development of the usual terminal symptoms, there was a great increase. The increase at this stage,

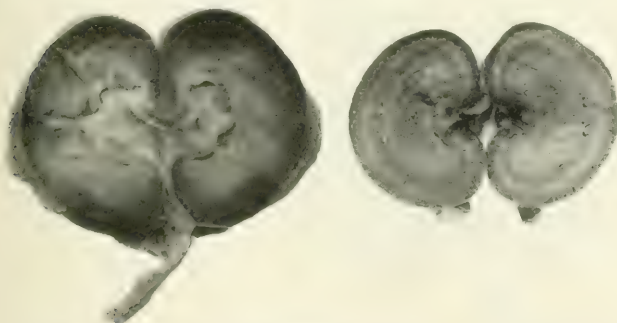


Fig. 3 (Dog 18).—The hydronephrotic kidney and the normal kidney (removed from opposite side) photographed on the same scale.

together with the low phenolsulphonephthalein output, are charted in Figure 2. There were, however, several important variations from this general type. Thus, Dog 17 showed a normal nitrogen content of the blood for sixteen days following the placing of the band about the ureter. In the suspicion that no obstruction had been created, an exploratory laparotomy was performed. It was found that at the site of the band a moderately thick ring of adhesions had formed. The ureter above this was definitely dilated and on palpation of the pelvis of the kidney, fluctuation was felt. The abdomen was at once closed and the observations continued as before. The determination of the incoagulable nitrogen in a sample of blood taken just before the operation showed 68 mg. per hundred c.c. Within seven days this had increased to 100 mg. per hundred c.c., and from then on there was a rapid rise until death. The question naturally arises as



to why, in this case, such an unusually long period elapsed before the cumulative phenomena appeared. Was it due to the fact that the hydronephrosis was mild and of slow development, or could it be that the obstruction was at first insufficient to produce any back-pressure, but later became so on account of contracting adhesions? Two facts indicate that the former was probably the case: First, there was a definite decrease in the phenolsulphonephthalein on the third and ninth days, showing that some change had taken place in the kidney; and second, at necropsy it was found that the pressure necessary to force fluid through the obstructed ureter amounted to 12 cm. of water—a very slight obstruction.

The most rapid rise occurred in Dog 16, in which the nitrogen content of the blood amounted to 168 mg. per hundred c.c. on the third



Fig. 4 (Dog 19).—The hydronephrotic kidney and the normal kidney (removed from opposite side) photographed on the same scale.

day after operation. At this time the animal was moderately toxic, vomiting several times. Venesection was performed on the fifth day, 225 c.c. of blood being removed. This was at once replaced by 150 c.c. of defibrinated blood, taken from a normal dog, and 100 c.c. of physiological saline solution. Within twenty-four hours there was a very sharp decrease in the incoagulable nitrogen, and from then until death, resulting from peritonitis, it was but slightly above normal. Associated with this rapid drop was a remarkable increase of the total nitrogen output in the urine.

The determination of the freezing point of the serum in a number of instances showed that there were but slight deviations from the normal when the nitrogen content was moderately increased; but with



the great accumulation of nitrogen preceding death the freezing point was considerably lowered.

The daily output of urine increased at once after the operation and continued so throughout the whole course. That this was a true polyuria is indicated by the fact that reducing the fluid intake did not immediately affect the total amount of urine. The specific gravity was correspondingly low. Faint traces of albumin appeared intermittently throughout. In the urine of but one dog (Dog 18) were casts found. The nitrogen output in the urine showed important variations. The average daily amount was approximately equal to the intake until the final stages, when a definite decrease is to be noted.

TABLE 1.—INTAKE AND OUTPUT OF NITROGEN DURING NON-TOXIC PERIOD

Dog	Time, days	Total Intake gm. N.	Average Daily Intake gm. N.	Total Urinary Output gm. N.	Average Daily Urinary Output gm. N.	Average Daily Loss of wt. gm.
10.....	16	80.9	5.05	85.17	5.32	37.5
17.....	21	99.1	4.58	52.3	3.92	76.2
18.....	25	101.3	4.05	58.1	3.92	44
19.....	19	62	3.26	68.1	3.58	71

TABLE 2.—INTAKE AND OUTPUT OF NITROGEN DURING TOXIC PERIOD

Dog	Time, days	Total Intake gm. N.	Average Daily Intake gm. N.	Total Urinary Output gm. N.	Average Daily Urinary Output gm. N.	Average Daily Loss of wt. gm.
10.....	4	0.6	0.15	11.19	2.79	387
17.....	6	6.47	1.08	15.8	2.63	350

In Table 1 is recorded the total amount of nitrogen excreted in the urine, as compared with that ingested, from the time of operation until the toxic symptoms developed; in the same manner the intake and output for the toxic period are shown in Table 2. In the case of Dogs 10 and 19 the output exceeded the intake, while with the other two the reverse took place. This bears no relation to the size of the animal or the loss of weight. The differences were slight, with one exception, Dog 17, in which the intake exceeded the output by 16.8 gm. This was not, however, accompanied by any marked increase in the non-protein nitrogen content of the blood.

During the terminal stages, although the nitrogen output greatly exceeded the intake, it did not equal the normal excretion during sim-

ple starvation.<sup>24</sup> This suggests that the great rise in the nitrogen content of the blood during this stage is due to a definite renal retention. A striking instance in which a low nitrogen excretion was accompanied by an accumulation of nitrogen in the blood is found in the case of

TABLE 3.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood			Δ
				H <sub>2</sub> O c.c.	N. gm.	Total Non-pro- tein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	
4/18	..	Normal .....	10.6	300	5.8	92	19	59	..
4/21	0	Operation .....	...	...	...	...	..	..	..
4/24	3	Good .....	...	300	5.8	122	86	70	..
4/25	4	Good .....	10.2	300	5.8	100	93	93	..
4/26	5	Refused food .....	...	600	1.8	116	103	88	..
4/27	6	Good .....	...	600	2.9	130	107	82	..
4/28	7	Good .....	...	600	5.8	136	..	..	..
4/29	8	Lively .....	...	800	5.8	99	56	56	..
4/30	9	Lively .....	9.7	800	5.8	110	64	58	..
5/ 1	10	Lively .....	9.5	400	5.8	132	92	70	..
5/ 2	11	Lively .....	9.5	400	5.8	104	69	66	..
5/ 3	12	Lively .....	9.5	300	5.8	...	..	..	..
5/ 4	13	Lively .....	9.4	300	5.8	100	87	87	..
5/ 5	14	Lively .....	9.3	300	5.8	...	..	..	..
5/ 6	15	Lively .....	...	450	5.8	116	78	68	.65
5/11	20	Lively .....	9.5	...	...	...	..	..	..
5/12	21	Lively .....	...	700	5.8	...	..	..	..
5/13	22	Lively .....	...	700	5.8	...	..	..	..
5/14	23	.....	9.6	700	5.8	86	59	69	..
5/15	24	Refused food .....	...	700	0.8	116	99	85	..
5/16	25	Vomiting .....	9.25	...	...	245	158	64	.75
5/17	26	Vomiting .....	8.45	...	...	...	...	..	..
5/18	27	Improved .....	...	300	0	305	250	82	.75
5/19	28	Very sick .....	8.05	400	0.6	395	180	71	.75
5/20	29	Died .....	...	...	...	...	..	..	..

Dog 16. On the third day after operation only 95 c.c. of urine were passed, despite the fact that water was forced. The nitrogen eliminated amounted to but 0.62 gm. Corresponding to this the incoagulable nitrogen in the blood rose from 66 to 178 mg. per hundred c.c.

24. Von Noorden, Carl: Metabolism and Practical Medicine, 1907, p. 292.

It was hoped that a careful study of the nitrogen intake and output might throw some light on the question as to whether the increase of incoagulable nitrogen in the blood is due to a (renal) retention or to metabolic disturbances characterized by an increased formation of

-OF Doc 10

Amt. Cals.	Sp. Gr.	Albumin	Sediment	Urine			Phthalein %		Lactose
				N. gm.	Urea N. gm.	Urea N. %	1 hr.	2 hrs.	
240	1.030	0	Neg.	4.44	...	..	70	..	6 hours
...	...	...	...	...	...	..	...	...	...
...	...	...	...	...	...	..	30	52	...
...	...	...	...	...	...	..	...	...	...
350	1.020	0	Neg.	4.13	2.9	72	..	..	8 hours
550	1.020	...	...	6.41	4.65	73	..	..	...
515	1.020	...	...	5.74	4.29	75	..	..	...
600	1.018	Trace	W. B. C.	6.35	4.12	65	8	22	...
580	1.012	...	...	6.09	3.81	62	..	..	8 hours
600	1.014	...	...	5.99	3.33	56	..	..	...
515	1.010	...	...	5.08	...	..	..	..	...
480	1.018	...	...	5.61	3.38	60	..	..	...
425	1.020	...	...	4.64	...	..	..	..	...
400	1.018	...	...	5.15	...	..	..	..	...
405	1.022	Trace	Neg.	5.50	...	..	..	..	...
405	1.022	...	...	5.39	...	..	21	38	...
...	...	...	...	...	...	..	..	37	...
535	1.017	Trace	Neg.	5.24	...	..	..	..	...
515	1.012	Trace	Neg.	4.39	...	..	..	..	...
470	1.018	...	...	5.20	...	..	..	..	10 hours
385	1.018	Trace	Neg.	4.26	...	..	..	..	...
620 (?)	1.010	Trace	Neg.	1.91	...	..	..	6	...
450	1.018	Trace	Pus	3.90	2.63	68	..	12	...
475	1.012	Trace	Pus	2.99	1.99	67	..	8	...
710	1.020	Trace	Pus	2.39	1.63	68	..	..	...
...	...	...	...	...	...	..	..	..	...

nitrogenous bodies. Bradford,<sup>25</sup> studying the changes in the nitrogen of the blood and urine following the removal of from two-thirds to three-fourths of the total kidney substance, expresses the opinion that

25. Bradford, J. R.: The Results Following Partial Nephrectomy and the Influence of the Kidney on Metabolism, Jour. Physiol., 1898-9, xxiii, 415.

TABLE 4.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood			
				H <sub>2</sub> O c.c.	N. gm.	Total Non-pro- tein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	△
		Normal .....	4.8	...	...	...	26	..	..
4/ 2	..	Operation .....	...	...	...	...	..	..	..
4/ 4	2	Good .....	...	...	...	...	..	..	..
4/ 6	4	Vomited .....	...	...	...	...	..	..	..
4/ 7	5	No vomiting .....	...	500	...	...	90	..	..
4/ 8	6	Improved .....	...	300	5.8	112	77	69	..
4/ 9	7	Good .....	...	550	5.8	...	88	..	..
4/15	13	Good .....	...	400	5.8	70	35	50	..
4/16	14	Good .....	4.4	300	5.8	...	..	..	..
4/17	15	Good .....	...	300	5.8	...	..	..	..
4/18	16	Good .....	...	...	...	...	35	..	..
4/19	17	Good .....	...	165	5.8	...	..	..	..
4/20	18	.....	...	250	5.8	67	39	58	..
4/21	19	Exploratory .....	...	...	...	...	..	..	..
4/23	21	Good .....	4.6	500	5.8	...	..	..	..
5/ 1	29	Good .....	4.5	400	5.8	68	40	59	..
5/ 6	34	Sick .....	4.2	300	0	...	117	..	..
5/ 7	35	Sick .....	...	300	...	276	..	..	0.74
5/ 8	36	Died .....	...	...	...	...	..	..	..

TABLE 5.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood			
				H <sub>2</sub> O c.c.	N. gm.	Total Non-pro- tein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	△
5/ 3	..	Normal .....	10.7	300	5.8	30	9	30	.58
5/ 4	..	Operation .....	...	300	5.8	29	13	46	..
5/ 5	1	Good .....	...	335	0	46	31	68	..
5/ 6	2	Good .....	10.5	450	5.8	66	43	65	..
5/ 7	3	Vomited .....	...	300	5.8	178	124	70	..
5/ 8	4	Improved* .....	...	1,000	1.0	188	122	65	..
5/ 9	5	Phlebotomy transfusion .....	...	600	0	...	84	..	..
5/ 9	..	Three hours after.....	...	...	...	...	61	..	..
5/10	6	Improved .....	...	1 050	6.4	...	25	..	..
5/11	7	Onset of peritonitis.....	9.	400	0	64	24	38	..
5/12	8	Peritonitis .....	...	650	5.8	...	27	..	..
5/13	9	Peritonitis .....	8.9	600	5.8	41	25	62	..
5/14	10	.....	8.95	...	...	...	..	..	..
5/15	..	Died .....	...	...	...	...	..	..	..

\* R. B. C., 6,200,000; Hb. 120 per cent.

mt. c.c.	Urine						Phthalein %		Lactose
	Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	1 hr.	2 hrs.	
..	.....	0	Neg.	....	....	..	75	..	6 hours
..	.....	.....	.....	....	....	..	..	..	.....
..	1.025	Trace	Neg.	....	....	..	..	40	.....
75	1.030	0	Neg.	....	....	..	..	48	9.5 hrs.
..	.....	.....	.....	....	....	..	..	..	.....
90	1.012	Trace	W. B. C.	....	....	..	26	..	.....
75	1.020	Trace	Few W. B. C.	6.65	5.27	79	..	..	.....
..	.....	.....	.....	....	....	..	30	42	.....
..	.....	.....	.....	....	....	..	..	..	.....
..	1.025	Trace	Neg.	....	....	..	..	..	8 hours
..	.....	.....	.....	....	....	..	..	..	.....
135	1.018	Trace	Neg.	5.15	....	..	..	..	.....
235	1.022	Trace	Neg.	4.04	....	..	..	..	.....
..	.....	.....	.....	....	....	..	..	..	.....
450	1.020	Trace	Neg.	....	....	..	..	..	.....
..	.....	.....	.....	....	....	..	15	41	.....
310	1.013	Trace	Neg.	....	....	..	..	..	.....
185	.....	.....	.....	0.02	....	..	..	0	.....
..	.....	.....	.....	....	....	..	..	..	.....

Amst. c.c.	Urine						Phthalein %		Lactose
	Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	1 hr.	2 hrs.	
140	1.038	0	Neg.	5.90	....	..	65	..	6 hours
155	1.043	0	Neg.	0.63	....	..	..	..	.....
130	1.030	.....	.....	2.93	2.10	71	..	70	.....
430	1.023	Trace	Neg.	8.15	6.40	78	..	50	.....
95	1.010	0	Neg.	0.62	0.55	88	..	3	.....
780	1.010	Trace	Neg.	4.88	3.57	73	..	42	.....
665	1.010	Trace	Neg.	3.37	2.55	76	..	..	.....
..	.....	.....	.....	....	....	..	..	..	.....
1,060	1.018	H	Neg.	9.34	8.89	95	..	45	.....
275	1.021	0	Neg.	7.93	....	..	..	..	.....
245	1.032	H	Neg.	9.2	....	..	..	..	.....
295	1.035	0	Neg.	9.34	....	..	..	..	.....
..	.....	.....	.....	....	....	..	..	..	8 hours
..	.....	.....	.....	....	....	..	..	..	.....

TABLE 6.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood			
				H <sub>2</sub> O c.c.	N. gm.	Total Non-pro- tein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	Δ
4-27	..	Normal .....	10.2	130	5.8	27	11	41	..
4-28	..	Normal .....	....	210	5.8	...	..	..	..
4-29	1	Operation .....	....	...	...	...	..	..	..
4-30	2	Good .....	....	300	0	36	17	47	..
5-1	3	Good .....	....	300	5.8	...	14	..	..
5-2	4	.....	....	225	0	...	..	..	..
5-3	5	.....	....	200	5.8	...	..	..	..
5-4	6	.....	....	200	5.8	...	..	..	..
5-5	7	.....	....	225	5.8	...	..	..	..
5-6	8	.....	....	100	5.8	...	..	..	..
5-7	9	.....	....	125	0	...	..	..	..
5-8	10	R. B. C. 7,200,000, Hb. 115 per cent.	....	290	5.8	...	..	..	..
5-9	11	Transfusion .....	....	300	5.8	...	12	..	0.62
5-10	12	Moderately sick .....	....	300	6.3	...	21	..	..
5-11	13	Improved .....	....	320	0	...	9	..	..
5-12	14	Good .....	9.85	220	5.8	...	..	..	..
5-13	15	Good .....	....	200	5.8	...	..	..	..
5-14	16	Exploratory .....	....	200	5.8	68	38	56	..
5-15	17	Good .....	....	300	0	...	27	..	..
5-16	18	Pulse 140, Temp. 39 C.	....	300	5.8	44	17	40	..
5-17	19	Good .....	....	400	5.8	...	..	..	..
5-18	20	Good .....	....	275	5.8	...	..	..	..
5-19	21	Pulse 132 .....	9.2	450	5.8	...	..	..	..
5-20	22	Pulse 140, Temp. 41 C.	....	300 (?)	5.8	...	..	..	..
5-21	23	Refused to eat .....	....	500	5.8	100	63	63	..
5-22	24	Improved .....	8.6	400	1.7	110	74	67	..
5-23	25	Improved .....	....	500	2.9	98	71	73	..
5-24	26	Good .....	8.35	400	0.87	...	..	..	..
5-25	27	Good .....	....	200	1.0	136	86	64	..
5-26	28	Vomited .....	....	320	...	...	..	..	..
5-27	29	Vomiting .....	....	300	...	185	131	71	..
5-28	30	Sleek .....	....	300	...	220	141	64	..
5-29	31	Very sleek .....	7.1	...	...	...	..	..	..
5-30	32	.....	....	500	...	...	..	..	..
5-31	33	.....	....	300	0	...	..	..	..
6-1	34	Died .....	....	...	...	...	..	..	..



F Dec 17

mt. no.	Urine						Phthalein %		Lactose
	Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	1 hr.	2 hrs.	
15	1.050	0	Neg.	5.72	4.49	78	63	..	6 hours
25	1.043	0	Neg.	5.59	....	..	..	..	.....
35	.....	.....	.....	.....	.....	..	..	..	.....
45	1.060	0	Neg.	....	....	..	..	..	.....
55	1.025	Trace	Neg.	5.69	4.56	79	27	68	.....
60	1.022	....	....	3.05	2.24	73	..	..	.....
65	1.028	....	....	4.04	....	..	..	..	.....
70	1.030	....	....	2.74	....	..	..	..	.....
75	1.030	0	Neg.	6.42	....	..	..	..	.....
79	1.034	....	....	5.64	....	..	..	..	.....
81	1.035	....	....	3.83	....	..	41	..	.....
85	1.040	....	....	4.19	....	..	..	..	.....
90	1.030	....	....	4.18	....	..	..	..	.....
100	1.026	....	....	2.55	1.82	71	..	..	.....
105	1.015	....	....	3.72	2.68	72	..	..	.....
110	1.032	....	....	3.10	....	..	..	..	.....
115	1.020	0	Neg.	3.40	....	..	..	..	.....
125	1.020	Trace	Neg.	3.72	....	..	..	..	.....
130	1.032	....	....	2.46	....	..	..	34	.....
145	1.015	....	....	4.40	....	..	..	37	.....
150	1.020	....	....	4.34	....	..	..	..	.....
165	1.024	....	....	3.96	....	..	..	..	.....
180	1.020	....	....	5.94	....	..	..	35	8 hours
185	1.010	....	....	2.40	....	..	..	..	.....
200	1.018	Trace	Pus cells	2.55	1.15	51	..	..	.....
210	1.017	....	....	3.72	2.15	58	..	20	.....
225	1.016	....	....	3.39	1.46	43	..	..	.....
235	1.017	....	....	2.35	....	..	..	..	.....
245	1.014	....	....	1.52	.59	38.5	..	..	.....
255	1.018	....	W. B. C.	1.82	1.05	58	..	..	.....
265	1.018	....	....	3.09	....	..	..	..	.....
275	.....	.....	.....	.....	.....	..	.....	5	.....
285	.....	.....	.....	.....	.....	..	.....	.....	.....
290	1.020	....	....	2.87	....	..	..	..	.....
300	1.010	..	Pus	0.97	....	..	.....	.....	.....
315	.....	.....	.....	.....	.....	..	..	..	.....

TABLE 7.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood				Δ
				H <sub>2</sub> O c.c.	N. gm.	Total Non-pro- tein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %		
5/22	..	Normal .....	5.15	300	5.8	...	..	..	..	..
5/23	..	Normal .....	....	300	5.8	34	14	41	..	..
5/24	..	Normal .....	....	300	5.8	...	..	..	..	..
5/25	..	Operation .....	....	...	...	...	...	..	..	..
5/26	..	Before operation .....	....	0	0	...	..	..	..	..
5/26	1	After operation .....	....	200	0	39	20	52	..	..
5/27	2	Good .....	....	300	3.2	55	27	50	..	..
5/28	3	Good .....	....	400	5.8	56	30	54	..	..
5/29	4	Good .....	....	300	5.8	74	43	58	..	..
5/30	5	Good .....	5.15	300	5.8	72	44	61	..	..
5/31	6	Good .....	....	350	3.8	...	..	..	..	..
6/ 1	7	Good .....	....	300	5.8	86	33	38	..	..
6/ 2	8	Good .....	....	300	4.6	...	..	..	..	..
6/ 3	9	Good .....	....	300	4.2	96	40	42	..	..
6/ 4	10	Good .....	....	300	4.2	...	..	..	..	..
6/ 5	11	Good .....	4.7	300	5.8	108	68	63	..	..
6/ 6	12	Good .....	....	300	3.8	...	..	..	..	..
6/ 7	13	.....	....	300	3.8	...	..	..	..	..
6/ 8	14	.....	4.65	300	4.6	90	49	54	..	..
6/ 9	15	.....	....	300	1.5	...	..	..	..	..
6/10	16	.....	4.75	300	4.9	...	43	..	..	..
6/11	17	.....	4.55	300	3.3	...	..	..	..	..
6/12	18	Distemper .....	4.45	300	1.6	81	42	50	..	..
6/13	19	Distemper .....	4.40	300	3.8	...	..	..	..	..
6/14	20	Distemper .....	4.25	150	1.0	...	..	..	..	..
6/15	21	Distemper .....	4.15	300	0.9	68	28	41	..	..
6/16	22	Distemper .....	4.05	300	5.8	...	..	..	..	..
6/17	23	Distemper .....	4.05	300	5.8	...	..	..	..	..
6/18	24	Distemper .....	4.05	300	5.8	92	48	52	..	.56
6/19	25	.....	....	300	5.8	114	60	53	..	.60
6/20	1	Sacrificed .....	....	...	...	...	..	..	..	..

\* Probable decomposition of urea after voiding.

Dec 18

Urine										Phthal- lein 2 hrs. %	Lac- tose
Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	NH <sub>3</sub> -N. gm.	NH <sub>3</sub> -N. %				
5	1.025	0	Neg.	4.82	3.78	78	...	...	95	6 hrs.	
5	1.020	0	Neg.	4.51	3.22	71	.21	4.6	..	.....	
5	1.023	0	Neg.	4.65	3.66	79	.26	5.5	..	.....	
	.....	.....	.....	.....	.....	..	...	.....	..	.....	
1	.....	.....	.....	0.52	0.37	71	...	.....	..	.....	
6	1.020	0	Neg.	0.86	0.49	58	...	.....	85	.....	
5	1.040	0	Few casts	2.83	.....	..	...	.....	40	.....	
5	1.030	Trace	Neg.	5.41	3.66	68	.5	9.3	62	.....	
50	1.027	0	Neg.	7.48	5.58	75	.78	10	55	.....	
5	1.025	0	Neg.	5.32	3.94	77	...	.....	58	.....	
50	1.025	Trace	Neg.	3.85	3.30	86	.39	10	..	.....	
50	1.020	0	Neg.	4.91	3.82	80	.19	4	32	.....	
5	1.020	0	Neg.	4.23	3.47	82	.23	5.5	..	.....	
50	1.028	0	Neg.	7.98	5.16	65	.57	12	75	.....	
50	1.020	Trace	Neg.	4.73	4.13	87	...	.....	..	8 hrs.	
50	1.018	Trace	Neg.	6.74	4.67	69	.87	12	45	.....	
10	1.015	Trace	Neg.	5.05	3.73	73	.31	6.2	..	.....	
50	1.020	Trace	Neg.	0.03	2.00	67	.94	31*	..	.....	
90	1.018	Trace	Neg.	3.41	1.93	57	...	.....	35	.....	
5	1.012	Trace	Neg.	2.32	1.07	42	.53	23*	..	.....	
50	1.018	0	Neg.	3.84	2.75	72	.48	12	35	.....	
5	1.012	Trace	Neg.	3.18	2.05	64	.43	12	..	.....	
5	1.015	Trace	Neg.	1.67	1.03	65	.19	11	15	8 hrs.	
5	1.015	Trace	Neg.	2.75	1.59	58	...	.....	20	.....	
55	1.015	Mod.	Neg.	2.37	1.95	82	...	.....	..	.....	
55	1.014	+	Pus	1.96	1.52	77	.14	7	..	.....	
50	1.020	+	Pus	4.92	3.66	74	.30	6	..	.....	
50	1.022	+	Pus	4.62	3.43	74	.43	9	43	.....	
55	1.025	+	Pus	4.61	3.71	80	...	.....	36	.....	
55	1.024	+	Pus	.....	.....	..	...	.....	50	.....	

the increased content in the blood is due to an excessive breaking down of tissue. Pearce,<sup>26</sup> studying the nitrogen excretion following the removal of three-fourths of the total kidney substance, states that no change takes place in the nitrogen metabolism other than that due to an inanition which results from the gastro-intestinal irritation constantly associated with extensive kidney reduction. We do not feel

TABLE 8.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood				Δ
				H <sub>2</sub> O c.c.	N. gm.	Total Non-pro- tein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %		
5/22	..	Normal .....	7.55	250	5.8	...	..	..	..	..
5/23	..	Normal .....	....	150	5.8	...	..	..	..	..
5/24	..	Normal .....	....	75	5.8	27	13	49	..	..
5/25	..	Operation .....	....	...	...	...	..	..	..	..
5/26	..	Before operation .....	....	200	0	...	..	..	..	..
	1	After operation .....	....	0	0	41	19	46	..	..
5/27	2	Good .....	....	300	5.8	...	29	..	..	..
5/28	3	Very lively* .....	....	400	5.3	30	46	51	..	..
5/29	4	Very lively .....	....	300	5.8	...	69	..	..	..
5/30	5	Very lively .....	....	300	5.8	102	69	68	..	..
5/31	6	Very lively .....	....	250	4.2	160	96	60	..	..
6/ 1	7	Very lively .....	7.20	300	1.3	96	63	66	..	..
6/ 2	8	Very lively .....	....	300	1.9	...	..	..	..	..
6/ 3	9	Very lively .....	....	300	3.9	68	53	78	..	..
6/ 4	10	Very lively .....	....	300	0.4	...	..	..	..	..
6/ 5	11	Very lively .....	7.20	300	5.8	76	43	57	..	..
6/ 6	12	Very lively .....	7.20	300	4.2	...	..	..	..	..
6/ 7	13	Very lively .....	7.20	300	5.8	...	..	..	..	..
6/ 8	14	Very lively .....	7.15	300	3.3	96	48	50	..	..
6/ 9	15	Very lively .....	7.00	300	0.9	94	41	44	..	..
6/10	16	Very lively .....	6.00	280	3.7	...	66	..	..	..
6/11	17	Very lively .....	6.80	315	1.0	...	..	..	..	..
6/12	18	Distemper .....	6.55	225	0.6	92	53	58	..	59
6/13	19	Distemper .....	6.40	300	2.9	108	57	53	..	66

\* See protocol.

that in our own experiments the nitrogen determinations during the non-toxic period offered conclusive evidence on this point,<sup>27</sup> although

26. Pearce, R. M.: Influence of a Reduction of Kidney Substance on Nitrogenous Metabolism, Jour. Exper. Med., 1908, x, 632.

27. Further work is planned for the study of this important point.

in several instances the tables show (particularly 7 and 8) nitrogenous equilibrium or even nitrogenous loss associated with a rise in the non-protein nitrogen of the blood. This would indicate an increased protein catabolism. During the terminal stages, however, there was a definite reduction in the nitrogen eliminated, indicating that the cumulative phenomena are due, in part at least, to retention.

OF Dog 19

Amt. cc.	Sp. Gr.	Urine							Phtha- lein 2 hrs. %	Lac- tose
		Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	NH <sub>3</sub> -N. gm.	NH <sub>3</sub> -N. %		
125	1.050	0	Neg.	6.09	4.90	80	...	....	..	.....
155	1.050	0	Neg.	8.81	6.09	69	...	....	88	4 hrs.
135	1.045	0	Neg.	5.74	5.30	92	.25	4.3	..	.....
1	.....	.....	.....	.....	.....	..	...	....	..	.....
23	.....	.....	.....	0.68	0.48	70	...	....	..	.....
65	1.055	0	Neg.	2.42	1.69	70	...	....	82	.....
230	1.030	0	Neg.	7.57	6.12	81	...	....	54	.....
240	1.025	0	Neg.	5.34	4.12	77	.38	7	50	.....
240	1.025	Trace	Neg.	5.35	4.71	88	.64	12	42	.....
280	1.020	0	Neg.	6.81	5.14	75	.57	8.4	..	.....
230	1.017	Trace	Neg.	2.51	1.94	77	.17	6.8	33	.....
265	1.018	0	Neg.	5.25	4.40	84	.44	8.2	50	.....
255	1.018	Trace	Neg.	3.62	2.73	75	.37	9	..	.....
235	1.022	Trace	Neg.	3.98	3.02	76	.35	9	35	.....
160	1.020	Trace	Neg.	2.57	2.06	80	.23	9	..	8 hrs.
265	1.023	Trace	Neg.	4.08	2.61	64	.41	10	30	.....
235	1.021	Trace	Neg.	3.22	2.81	87	.37	11	..	.....
260	1.020	Trace	Neg.	2.80	2.45	87	...	....	..	.....
290	1.018	Trace	Neg.	3.13	2.26	72	.34	11	15	.....
90	1.013	Trace	Neg.	0.87	0.64	73	.13	15	..	.....
215	1.016	Trace	Neg.	2.12	1.48	69	.23	11	26	.....
290	1.012	Trace	Neg.	2.00	1.24	62	.11	6	..	.....
290	1.016	Trace	Neg.	1.83	1.60	87	...	....	16	10 hrs.
237	1.018	Trace	Neg.	2.19	1.51	69	.36	16	14	.....

The phenolsulphonephthalein test has proved to be very sensitive in these cases, since in the earliest stages there is a slowing of the excretion and in the later stages a progressive reduction in the total. Normally in dogs there is excreted during the first hour from 60 to 70 per cent. of the amount injected, while during the second hour

an additional 15 to 20 per cent. is recovered. The first change noted in these cases was a reduction of the amount excreted in the first hour with a corresponding increase during the second hour, the total for two hours thus approaching normal. In the case of four of the dogs the phenolsulphonephthalein test was made daily following operation, and it is seen that within forty-eight hours there was a moderate reduction, the average total being 53 per cent. This corresponds to the increased nitrogen content of the blood. Coincident with the development of toxic symptoms, or with a marked diminution of urinary nitrogen, there was a low total excretion without exception. This is very striking. Attention is called to the suddenness with which marked functional changes took place in several instances. Thus, in Dog 16, within twenty-four hours the total phenolsulphonephthalein excretion dropped from 50 per cent. to 3 per cent., and during this time toxic symptoms appeared. At the end of the next twenty-four hours the general condition was improved and the phenolsulphonephthalein excretion was 42 per cent.

The only deviation from normal in the excretion of lactose was a moderate delay, the longest being ten hours.

The phloridzin test was performed as follows: Dog 14, on the second, fourteenth and twenty-fourth days after the operation; Dog 10, on the seventh and twentieth days, and Dog 18, on the twenty-fourth day. Without exception reducing bodies were present in the urine in large amounts before the expiration of half an hour from the time of injection. This corresponds with the normal as determined before the operation in each case.

#### PATHOLOGICAL CONSIDERATION

In each of the eight experiments a hydronephrosis developed as a result of the ureteral obstruction. The pressure necessary to overcome this resistance varied from 12 to 70 cm. of water. In every case, grossly, the ureter was tortuous and markedly dilated from the kidney to the point of obstruction, and the kidney was larger than the one previously removed from the opposite side, with dilatation of the pelvis and flattening of the calices. The distention of the capsular veins was always prominent, but varied considerably in degree. Thus, in Dog 18, the capsule was smooth and normal in color, only a vein here and there being noticeably engorged; while, on the other hand, the kidney of Dog 19 was covered with a network of large and tortuous vessels. In one instance, Dog 16, the kidney showed, microscopically, a beginning atrophy of the parenchyma, with only a slight dilatation of the collecting tubules, although, in the gross, the pelvis was distended and the calices flattened.



Infection of the pelvis of the kidney occurred in five of the eight dogs studied. It is significant that those which did not develop an infection had the shortest duration of life, after operation. Four cases, 10, 14, 17 and 18, showed pus in the urine for several days before death, and in these the pyelonephritis was very marked. In the remaining animal, Dog 19, the infection was slight, and the urine showed no pus. In Dogs 14, 18 and 19, there were no signs of cystitis. Thus it will be seen that in those cases in which sufficient time elapsed a pyelonephritis developed, and that three were unaccompanied by cystitis.

#### CONCLUSIONS

1. Incomplete ureteral obstruction in dogs, causing a back pressure of from 12 to 30 cm. of water, results in the development of a hydronephrosis.

2. This hydronephrosis causes a definite disturbance of renal function, characterized by polyuria, traces of albumin, diminished output of phenolsulphonephthalein and delayed excretion of lactose. There is no delay in the appearance of a glycosuria after the injection of phloridzin.

3. When one kidney is removed from an animal and the foregoing functional changes are brought about in the remaining organ, by the production of a hydronephrosis, the non-protein nitrogen content of the blood rises, and remains at this increased level (with slight variations) for a considerable period of time, unassociated with toxic symptoms.

4. This gives place to a sudden, severe, renal insufficiency, rapidly fatal, and characterized by marked toxemia, great increase in nitrogen content of the blood and very low phenolsulphonephthalein output.

5. During this final stage of renal insufficiency, caused by back-pressure alone, or by back-pressure with superimposed infection, there is a true nitrogen retention.

6. Under the conditions established in these experiments the occurrence of pyelonephritis is only a question of time; the animals which came to necropsy within ten days of the operation showed no signs of infection.

We wish to express our gratitude to Dr. L. G. Rowntree for his interest and helpful suggestions, and to Dr. M. C. Winternitz for his kindness in examining the pathological specimens and dictating the histological notes.

#### APPENDIX: HISTOLOGICAL NOTES ON THE AFFECTED KIDNEYS

Dog 10.—Marked, general, polymorphonuclear infiltration, the infection ascending from the pelvis and invading the cortex, overshadowing other changes that may be present. Definite dilatation of the glomeruli, with retraction of the tufts, and apparently some dilatation of the tubules.

Dog 14.—Infection in the pelvis, ascending into the pyramids, where there is a deposition of calcium salts. The pyramids are moderately flattened and the tubules dilated. In the cortex there are a few areas in which the tubules are dilated and filled with material suggesting forming casts. For the most part, in the cortex, the tubules are not widened, the lumina being small, and the epithelium somewhat swollen. One small but typical arteriosclerotic scar is seen.

Dog 16.—There is a striking beginning atrophy of the cortex, with a uniform decrease in size of the tubules. The glomeruli remain unchanged. Slight dilatation of the pyramid tubules. No signs of infection in the pelvis.

Dog 17.—Severe infection of the pelvis, ascending into the cortex, and obscuring other changes. There is seen, however, to be definite dilatation of the glomeruli with shrinking of the tuft.

Dog 18.—There is marked infiltration with polymorphonuclear leukocytes, running in streaks from the cortex to the pelvis. The glomeruli are moderately dilated, the capsular space being more conspicuous than usual. The tubules are everywhere dilated, without any flattening of the epithelium, the latter being swollen and coarsely granular, with irregular and serrated edges. In the lumen is a small amount of serum.

Dog 19.—There is a very slight infection in the pelvis and pyramids. The pyramidal tubules are less dilated than are the cortical ones. Just beneath the capsule there is a definite fibrosis of the cortex, and in this zone most of the glomeruli and tubules are atrophied, although there remain a few dilated canals. In the rest of the cortex the tubules are considerably dilated, the epithelium flattened and the lumina contain granular material. The glomeruli are widely distended and the tufts retracted. There are seen a few fibrous scars along the course of the interlobular vessels, but there is no arterial thickening.

FURTHER OBSERVATIONS ON THE EMPLOYMENT OF  
SPECIFIC AND NON-SPECIFIC ANTIGENS IN THE  
PERFORMANCE OF THE GONOCOCCIC  
COMPLEMENT-FIXATION TEST \*

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In a former paper<sup>1</sup> read before the Philadelphia County Medical Society May 28, 1913, it was conclusively shown by Thomas and Ivy in an analysis of over 200 cases in which monovalent, trivalent, hexavalent and a commercial antigen of twelve strains of gonococci were employed, that the gonococcus complement-fixation test possesses great specificity so far as positive results are concerned. The results have proved that "the different strains of the gonococcus differ markedly one from another—so much so that the antibodies produced in the body by the toxin of one strain will in many instances not bind the complement in the presence of an antigen prepared from another strain. Therefore, if only one strain is used in the preparation of the antigen, a great many negative results would be obtained in positive cases; an antigen prepared from many strains fixes the complement whenever one of its component strains does so, and consequently the necessity of testing a serum against a number of antigens separately is avoided. It is not to be denied that there probably are other strains of gonococci differing widely from any present in the polyvalent antigen, so that at times a negative result will be obtained in a positive case."

Convinced from our previous study of the specificity of the gonococcus complement-fixation test in gonorrheal infections, namely, that although a negative reaction may be obtained in gonorrheal subjects and consequently is devoid of reliance, a positive reaction is most dependable and was not obtained in a large series of infectious and other diseases.

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\* Read before the Philadelphia Pathological Society, May 28, 1914.

\* From the Department of Genito-Urinary Surgery and Laboratories, Polyclinic Hospital, and the William Pepper Laboratory of Clinical Medicine.

1. Thomas, B. A., and Ivy, Robert H.: The Gonococcus Complement-Fixation Test and Analysis of Results from its Use, *THE ARCHIVES INT. MED.*, 1914, xiii, 143.

In this article, in view of the finding of many Gram-positive and Gram-negative bacteria in the urine after massage of the prostate gland and seminal vesicles in the involvement of these organs in neisserian infection, a study has been made with respect to determining the specificity of the gonococcus antigen in the complement-fixation test by employing non-specific antigens made up from the various bacteria isolated from time to time.

Antigens were prepared from the following micro-organisms and utilized routinely in a series of serums from gonorrheal subjects:

Nine strains of gonococci.<sup>2</sup>

Fifteen strains of meningococci.<sup>2</sup>

Six strains of streptococci.

Six strains of the *Micrococcus albus*.

Six strains of the pneumococcus.

Six strains of *Micrococcus aureus*.

Three strains of the *Micrococcus catarrhalis*.<sup>2</sup>

Six strains of *Corynebacterium pseudodiphtheriticum*.

Six strains of *Bacillus coli*.

#### TECHNIC OF THE PREPARATION OF THE ANTIGENS

As in the former work the best results were obtained with antigens prepared in the following manner:

Forty-eight-hour old cultures were washed off in sterile distilled water, shaken for one hour, and autolyzed for twenty-four hours in a thermostat at the temperature of 37 C. and heated in a water-bath at 60 C. for one-half hour. Before use this antigen is diluted 1:10 by the addition of 0.85 per cent. salt solution. The quantities of each antigen used is determined by preliminary standardization. The technic on which we have learned to place the greatest reliance is essentially the same as that employed by us in the performance of the Wassermann reaction — substituting the specific or non-specific antigen in each case for the syphilitic antigen, using always the carefully standardized single unit of complement and the routine standardization of antigen and amboceptor. This technic is fully described in the former paper on this subject.

Two hundred and sixteen serums in all were tested by the employment of various non-specific antigens. These added to the results of the previous work number 420 serums in which the complement-fixa-

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2. We are indebted to Dr. Parks of the Research Laboratory, New York Department of Health, for the fifteen strains of meningococci and the three strains of *Micrococcus catarrhalis*, and to Dr. A. P. Hitchens of H. K. Mulford Company for the nine strains of gonococci employed in this work.

tion test has been employed, using specific gonococcus and non-specific antigens.<sup>3</sup>

Of the 216 cases in which both the specific and non-specific antigens were employed, we have grouped the cases according to their clinical diagnoses.

1. Patients clinically cured, 9 cases.
2. Acute anterior urethritis, 10 cases.
3. Acute and subacute anteroposterior urethritis, 40 cases.
4. Chronic posterior urethritis, 84 cases.
5. Stricture, 7 cases.
6. Epididymitis, 30 cases.
7. Arthritis, 30 cases.
8. Gynecological affections, 3 cases.
9. Vulvovaginitis, 1 case.
10. Sexual impotence, 2 cases.

RESULTS OF COMPLEMENT-FIXATION REACTIONS WITH SPECIFIC GONOCOCCIC AND NON-SPECIFIC ANTIGENS IN TWO HUNDRED AND SIXTEEN CASES

Antigens	No. Cases	Results	
		No Positive	No. Negative
Specific; Gonococcic:			
Nonvalent .....	216	67	149
Parke, Davis & Co. ....	216	67	149
Non-Specific:			
<i>Micrococcus catarrhalis</i> .....	180	5	175
<i>Pneumococcus</i> .....	216	4	212
<i>Micrococcus aureus</i> .....	216	3	213
<i>Streptococcus</i> .....	216	1	215
<i>Corynebacterium pseudodiphtheriticum</i> .....	160	1	159
<i>Meningococcus</i> .....	216	1	215
<i>Micrococcus albus</i> .....	216	....	216
<i>Bacillus coli</i> .....	160	....	160

Of this series of cases 135 serums gave negative results with the employment of specific and non-specific antigens.

Sixty-seven serums gave positive results with specific gonococcus antigens.

Fifteen serums gave positive results with non-specific antigens.

Of the complement-fixation tests, using non-specific antigens, the *Micrococcus catarrhalis* antigen gave positive results in 5 cases, the pneumococcus in 4, the *Micrococcus aureus* in 3, the streptococcus in 1, the *Corynebacterium pseudodiphtheriticum* in 1 and the meningococcus in 1 case.

3. Standardization of all the specific and non-specific antigens at the conclusion of this study as compared with their antigenic properties in the beginning demonstrated no deterioration.

Four of the foregoing non-specific antigens gave positive results when all other non-specific and specific antigens resulted negatively. They were:

1. *Pneumococcus*, 4 cases.
2. *M. aureus*, 3 cases.
3. *M. catarrhalis*, 1 case.
4. *Corynebacterium pseudodiphtheriticum*, 1 case.

Six of the foregoing fifteen non-specific fixation reactions occurred conjointly with the specific fixation reaction. They were:

The *Micrococcus catarrhalis*, 4 cases.

The streptococcus, 1 case.

The meningococcus, 1 case.

Our explanation for these occurrences in the complement-fixation reaction is that frequently a mixed infection complicates the gonorrheal urethritis, prostatitis, seminal vesiculitis, etc., also that not infrequently the gonococcus has ceased to be viable and that the active cause for the inflammation is a superimposed bacterium.

#### CONCLUSIONS

1. Although mixed infections are commonly found, antibodies of the non-specific organisms rarely bind complement in the presence of the non-specific antigens, and when such is the case, it can be attributed to the implantation of a superimposed mixed infection.

2. The specificity of the gonococcus complement-fixation test when positive in cases of neisserian infection seems to be clearly established; a negative reaction, on the contrary, means absolutely nothing from the clinical point of view.

3. Those organisms in cases of mixed infection capable of binding complement in our studies have been the *Micrococcus catarrhalis*, the pneumococcus, the *Micrococcus aureus*, the streptococcus, the *Corynebacterium pseudodiphtheriticum* and the meningococcus.

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## HOW SHALL WE TELL WHETHER OR NOT THE MYOCARDIUM IS COMPETENT?\*

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The determination of the functional capacity of the vital organs is a problem that is of the utmost interest in prognosis. If a man consults a physician for symptoms pointing to disturbance of the heart, the kidneys or the liver it would be of great advantage not only to the patient, but also to his advisor if some satisfactory means were known by which the power of the affected organ to do its work could be determined. So far as concerns the kidneys and the liver, fairly reliable functional tests are at our disposal. Are we able to say as much of the myocardium? For example, a man, aged 50 or more years, presents himself in the consulting room complaining of dyspnea, or perhaps of some symptom less definitely associated with myocardial insufficiency. He proves to be a modern business man with important obligations. He has lived the life of his class: He has been a large and irregular eater and his diet has contained an overproportion of protein or of carbohydrate food, depending on his individual preference; he has drunk little or no water, two or three or more cups of coffee or tea, or of coffee and tea; more or less alcohol; sometimes malt liquors, sometimes distilled liquors, sometimes wine, again a liberal amount of all. He has smoked from eight to ten cigars a day. He has always slept well; but perhaps now he is beginning to have trouble in getting to sleep, or, provided he goes to sleep promptly, he soon awakens and is restless. His bowels, which have always been regular, are beginning to require attention. He has to get up once or twice at night to urinate, and for thirty years he has not taken any more exercise than was absolutely necessary. In the course of the physical examination you find him to be overweight; you find that he is beginning to develop a definite pulmonary emphysema; that his heart is larger than it should be and that the rate is a little accelerated, but that it presents no endocardial murmurs; that his blood-pressure is a trifle higher than it should be, and that his urine is increased in quantity and is of low specific gravity, but shows neither albumin nor casts. Let us suppose that the cardiac hypertrophy in such a case seems to be the important

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pathologic finding; can we determine by any means the capacity of the myocardium of that individual?

The following tests have been advocated from time to time for this purpose:

1. The increase in the pulse-rate between the recumbent posture and the erect posture.
2. The increase in the pulse-rate after slowly flexing and extending the right forearm (*Selbsthemmungsprobe* of Herz).
3. The increase of the systolic blood-pressure on constricting the femoral arteries, proposed by Katzenstein.
4. The increase of the systolic blood-pressure after certain exercises, proposed by Graupner.

The determination of the change in pulse-rate on assuming the erect from the recumbent posture and after flexing and extending the right forearm a definite number of times is clinically easy of execution and may be applied equally well to patients of both sexes. The determination of increase of the systolic blood-pressure after constriction of the femoral arteries is less readily performed and is impossible in the case of female patients who are being examined in the physician's office. The procedure of Graupner requires a piece of apparatus which is not well adapted to the ordinary consulting room.

With the introduction of the auscultatory method of blood-pressure determinations it has been possible clinically to determine the diastolic pressure, and consequently the pulse-pressure, with accuracy. Hence it has become possible to determine certain mathematical formulas which indicate the conditions under which the circulation is being carried on.

Tigerstedt<sup>1</sup> has suggested a formula for determining the efficiency of the heart as a pump. The pulse-pressure multiplied by the pulse-rate gives the velocity of the circulation. The systolic pressure multiplied by the pulse-rate gives the work of the heart. The velocity of the circulation divided by the work of the heart, according to Tigerstedt, gives the efficiency of the heart as a pump.

$$\frac{\text{Pulse-pressure} \times \text{pulse-rate} = \text{velocity}}{\text{Systolic pressure} \times \text{pulse-rate} = \text{work}} = \text{efficiency of the heart as a pump.}$$

In other words, the pulse-pressure, divided by the systolic pressure. In a normal person this coefficient is from 25 per cent. to 35 per cent. In a normal person in whom the systolic pressure was 126 mm. and the diastolic pressure was 81 mm. obtained by the auscultatory method, the pulse-pressure was 45 mm. and the cardiac efficiency was 35 per cent.

1. Tigerstedt: In Hirschfelder: Diseases of the Heart and Aorta, 1910, Ed. 1, p. 26.

Many authors have agreed that the second phase (the murmur phase) of the auscultatory blood-pressure observation indicates cardiac strength (Tornai,<sup>2</sup> Fischer,<sup>3</sup> Goodman and Howell<sup>4</sup>).

Goodman and Howell<sup>4</sup> have shown that the second and third phases of the auscultatory blood-pressure indicate cardiac strength, and that the first phase and the fourth phase indicate cardiac weakness. They have suggested that by determining the percentage of the pulse-pressure formed by the different phases and adding the second and third phases together and the first and fourth phases together, a proportion could be determined which would give an idea of the relative cardiac strength and cardiac weakness factors. They found that when the cardiac weakness factor was in excess of the cardiac strength factor there was evidence of inefficiency of the myocardium. In a normal person they found the following percentages: Pulse-pressure, 45 mm.

First phase .....	31.1 per cent.
Second phase .....	44.4 per cent.
Third phase .....	11.1 per cent.
Fourth phase .....	13.3 per cent.

99.9 per cent.

C. S. : C. W. :: 55.5 : 44.4

Stone<sup>5</sup> has suggested the determination of a cardiac load and overload factor based on auscultatory blood-pressure determinations. He pointed out that in sixty-one normal persons with an average systolic pressure of 123 mm. and an average diastolic pressure of 80 mm., the pulse-pressure average was 40 mm.

"The amount of energy expended, therefore, to maintain the circulation in excess of that required to open the aortic valves and overcome the resisting pressure of 80, was 40. The normal load may, therefore, be considered to be

$\frac{40}{80}$   
 — or 50 per cent. of the diastolic pressure."

He has shown that in fourteen cases of decompensated myocardial disease the load was 76 per cent., an overload of 26 per cent. In fifty-one cases of arterial hypertension the load was 69 per cent., an overload of 19 per cent. He says that an overload factor of 50 per cent. indicates that there is impending danger of myocardial exhaustion.

In this paper I have compared the variations in the pulse-rate in the recumbent and in the erect posture, the cardiac efficiency factor of Tigerstedt, the percentage of the pulse-pressure formed by the second

2. Tornai: *Ztschr. f. diät. u. physik. Therap.*, xiii, 809; abstr., *Deutsch. med. Wchnschr.*, 1909, xxxv, 2287.

3. Fischer: *Deutsch. med. Wchnschr.*, 1908, xxxiv, 1141.

4. Goodman and Howell: *Univ. Penn. Med. Bull.*, 1910, xxiii, 469; *Am. Jour. Med. Sc.*, 1911, cxlii, 334.

5. Stone, Willard, D.: *The Clinical Significance of High and Low Pulse-Pressures, with Special Reference to Cardiac Load and Overload*, *Jour. Am. Med. Assn.*, 1913, lxi, 1256.

phase of the auscultatory blood-pressure reading, the C. S. : C. W. ratio of Goodman and Howell and the cardiac overload factor of Stone in ten fatal cases of cardiac and cardiorenal disease; in seven cases of compensated cardiac disease; in six cases of cardiac decompensation which subsequently had compensation restored; in eight cases of chronic interstitial nephritis in which the patients are still living, and in nine cases of various diseases in which the functional capacity of the myocardium was of importance in prognosis.

The blood-pressure observations were all made in the recumbent posture, with a 12 cm. cuff. In the tables, those marked \* were made with a Tycos instrument, those marked † were made with a Riva Rocci and those marked § were made with a Stanton instrument. The auscultatory method was employed in every case. The first point, the appearance of the first tap, was recorded as the systolic pressure; and the fifth point, the disappearance of all sounds, was recorded as the diastolic pressure. In the tables — (minus) means that the observation was not made; + means that the formula could not be worked out.

In ten cases of cardiorenal disease fifty-three observations were made (Table 1). At many of these observations the difference in pulse-rate between the recumbent and the erect posture could not be obtained because the patients were confined to bed. At none at which the observation could be made was the increase excessive. It is significant that at two observations the pulse-rate decreased when the patient stood; in Case 424 there was a decrease of two beats; in Case 215 there was a decrease of six beats.

The cardiac efficiency factor was above 35 at forty-four observations. Once it was 35. In Case 105, a patient with chronic interstitial nephritis, pleural effusion, hypertrophy and dilatation of the heart, the factor was within normal limits three times and once it was much below normal, 19 per cent. The last record in this patient was made eight months before his death and the symptoms were more those of pleural effusion at the times at which I saw the patient than they were those of cardiac failure. In Case 180 likewise, although the patient died of uremia and the necropsy showed chronic parenchymatous nephritis, the symptomatology was that of indefinite abdominal disease (a chronic duodenal ulcer was found at necropsy) and the myocardium was not considered seriously impaired. The very high cardiac efficiency factor in Case 424 and in Case 511 is interesting in view of the fatal termination in two months in the one and within twenty-four hours in the other.

The second phase of the blood-pressure in these cases was below 40 per cent. of the pulse-pressure, when it could be worked out at every observation except four. In Case 215 the second observation,

TABLE 1.—BLOOD-PRESSURE OBSERVATIONS IN TEN FATAL CASES OF CARDIORENAL DISEASE

Date	Reum- bent	Erect	C. E.	Second phase	C. S. : C. W.	Over- load	Remarks
2/ 5/12	—	—	42 <sup>%</sup>	3.5 <sup>%</sup>	+	23	Fibroid myocarditis.
2/13/12	82	90 <sup>1</sup>	49	14.0	+	46	This observation of the pulse was made in the sitting posture.
2/19/12	76	—	39	14.8	22.2 : 77.5	15	
2/27/12	88	—	41	22.5	+	20	
3/ 8/12	—	—	43	12.9	+	25	
3/14/12	—	—	37	16.0	+	9	Tincture digitalis, 5 drops, nitroglycerin 1/100 grain four hours, begun 3/12/12.
3/18/12	—	—	48	11.4	71.4 : 28.5	44	Tincture digitalis stopped. Patient died three weeks after this observation.
5/ 2/12	54	—	38	17.6	+	11	Chronic parenchymatous nephritis. Cerebral thrombosis occurred to-day. Admitted to hospital.
5/ 3/12	52	—	34	9.6	+	2	
5/ 4/12	50	—	38	29.4	+	11	
5/10/12	44	—	44	+	+	30	
5/17/12	61	69 <sup>1</sup>	47	30.0	+	38	This observation of the pulse was made in the sitting posture. Improved sufficiently to leave hospital.
6/ 8/12	84	88	42	37.5	+	22	
6 15/12	84	86	36	31.4	+	8	The patient died twenty-three days after this observation was made.
2/20/12	92	—	30	+	+	-7	Chronic interstitial nephritis.
2/28/12	100	—	19	21	+	-26	
7 13/12	84 <sup>1</sup>	88	27	52.6	+	-12	This observation of the pulse was made in the sitting posture. The patient died eight months later.
8 11/12	106	—	26	+	+	-15	
8 25/12*	82	82	29	22.7	+	-8	Chronic parenchymatous nephritis.
9/16/12†	84	—	31	13.6	+	-6	After three weeks hospital treatment.
9/26/12†	94	100	37	52.9	76.4 : 23.4	10	Feeling well.
6/ 6/13†	84	98	29	56.8	81.8 : 18.0	-9	Abdominal pain, nausea and vomiting and vertigo.
6 15/13†	88	98	30	34.2	44.7 : 55.2	-6	Edema of the ankles, suborbital puffiness, tingling in fingers. Died seven months later.
11/19/12	82	76	42	29.0	58.0 : 41.7	24	Angina pectoris.
11/29/12	70	72	35	57.1	67.3 : 32.6	4	After four brine baths 98 F. Death about four weeks later.
11/ 4/12	122	—	44	9.4	71.6 : 28.2	30	Mitral regurgitation.
12/13/12	110	—	39	+	+	14	The patient died the next day.
1/ 8/13*	86	—	47	30.0	+	40	Chronic interstitial nephritis.
1/10/13*	78	—	45	39.0	82.9 : 17.0	32	Patient in bed improving under treatment.
1/15/13*	80	—	41	38.8	49.9 : 49.9	22	
2/ 2/13*	64	—	50	13.0	86.9 : 12.19	52	Patient doing well.
3/ 3/13*	72	—	49	20.4	+	48	Patient up and about, feeling well.
3/20/13*	—	—	50	7.0	85.9 : 13.9	50	Before a brine bath.
4/11/13*	—	—	49	9.0	+	46	After a brine bath.
4/21/13*	78	—	45	20.4	79.5 : 20.3	33	
5 1/13*	78	—	44	15.2	28.2 : 71.7	29	The brine baths do not agree with her; feels exhausted and does not sleep well.

In this and the following tables the observations made with the Tyco's instrument are marked \*, those with the Riva-Rocci †, and those with the Stanton instrument §. The minus sign means that the observation was not made. The is sign means that the formula could not be worked out.

TABLE 1.—(Continued)

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
239	10/ 1/18†	82	—	% 52	% 12.0	87 : 13	% 61	The patient is not feeling well.
	11/29/18†	76	—	51	5.2	20.9 : 78.8	55	
	12/17/18†	86	86	48	23.7	90.7 : 0.2	42	Nausea.
	1/11/14*	78	—	41	16.6	+	22	Fairly well.
	1/31/14*	—	—	43	+	+	26	Beginning of last illness. Renal dyspnea, nausea and vomiting.
	2/ 5/14*	82	—	46	25.5	85.9 : 13.8	36	Pulmonary edema.
	2/12/14*	80	—	42	2.4	+	24	Temporary improvement.
	3/18/14*	82	—	39	20.5	+	15	Patient not so well. Death one week later.
414*	11/11/13	100	—	48	39.2	+	42	Auricular fibrillation.
	12/ 1/13	92	—	36	2.9	+	6	Nephritis.
	12/ 4/13	76	—	49	+	+	48	
	12/ 8/13	74	—	51	+	+	58	
	12/13/13	86	—	48	+	+	35	
	12/14/13	80	—	45	33.3	+	31	Cerebral thrombus.
	1/ 7/14	70	—	42	35.0	+	22	Some improvement in symptoms. The patient died about one month later.
	11/24/13	90	88	58	+	+	88	Mitral regurgitation. The patient died two months later.
511*	4/11/14	92	—	72	18.7	81.2 : 18.7	216	Uremia. The patient died the next mornl.g.

which gave a percentage of 57.1, was made during a temporary improvement in the patient's condition.

The C. S. : C. W. ratio could be worked out at only twenty of these observations. The C. S. was greater than the C. W. factor at fifteen observations, and the two were equal once. At four observations the C. W. factor was greater than the C. S. factor. In the majority of the cases an absent point in the auscultatory blood-pressure determination makes it impossible to work out this proportion.

The cardiac overload factor was demonstrable in all cases except Case 105 and Case 108. In these the cardiac load was below 50 and gave a negative overload factor. In both of these cases the pulse-pressure was low. In Case 424 the overload amounted to 88 per cent.; in Case 511 to 216 per cent.

In seven compensated heart cases (Table 2) thirty-nine observations were made. In none was it possible to say that active decompensation was present. In Case 15 the chief complaint was weakness; in Case 127 it was a sensation of being tired; in Case 129 nervousness; in Case 176, weakness; in Case 275, rapid pulse; in Case 277, retrosternal pain; in Case 419, dyspnea.



TABLE 2.—COMPENSATED HEART CASES

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
155	1/10/11	—	—	40	52.2	+	18	Parenchymatous myocarditis. Carbonated brine baths being given.
	1/12/11	—	—	34	+	+	6	
	1/14/11	—	—	44	63.2	71.3 : 28.5	31	
	1/16/11	—	—	52	28.3	36.9 : 46.6	59	
	1/18/11	—	—	45	8.5	+	32	
	1/20/11	—	—	39	26.1	73.7 : 26.1	15	Carbonated brine baths finished. Resistance exercises begun.
	1/21/11	68	90	46	29.0	43.5 : 56.3	37	
	2/13/11	—	—	56	10.9	51.5 : 48.4	78	
	2/20/11	—	—	50	48.2	85.7 : 14.2	53	
	2/27/11	—	—	43	46.9	69.3 : 30.5	35	
	3/ 6/11	—	—	50	46.2	+	51	
127	3/13/11	—	—	40	44.4	55.5 : 44.4	18	Resistance exercises finished.
	4/18/12*	96	104	31	26	+	-4	Mitral regurgitation.
	5/11/12*	74	—	38	82	84 : 16	12	During an attack of acute bronchitis. Digitalis 10 drops p. c.
	10/31/13†	80	90	24	56.6	+	-19	
	11/ 7/13†	72	80	36	43.7	62.4 : 37.4	8	
	11/14/13†	90	—	38	30.7	49.9 : 49.9	12	
129	4/23/12*	80	90	43	23.3	83.3 : 6.6	26	Mitral regurgitation.
	5/23/12*	90	100	46	30.4	+	0	
	2/15/13†	78	100	44	31.0	65.3 : 34.3	30	
	9/ 8/13†	88	108	37	55.5	+	10	
	1/13/11§	76	90	43	23.3	62.2 : 37.7	31	Parenchymatous myocarditis.
176	1/27/11§	70	80	39	27.9	55.8 : 44.1	15	
	2/10/11§	84	86	40	22.7	61.8 : 38.5	18	After a course of carbonated brine baths.
	2/16/11§	70	82	41	22.9	+	19	
	8/11/12*	64	78	40	18.1	+	16	
	8/13/13*	72	90	36	48.5	68.5 : 31.3	8	
227†	3/10/13	86	108	42	17.6	74.0 : 25.8	44	Angina pectoris.
	1/28/14	94	110	40	+	+	16	In the interval the patient had had a cerebral embolism.
275	13/ 5/13*	72	92	35	+	+	-8	Parenchymatous myocarditis. Carbonated brine baths begun.
	3/20/13*	68	—	35	+	+	-8	
	3/30/13*	—	—	39	20	72 : 25	14	
	4/ 4/13†	92	114	23	50	75 : 24.6	-20	Carbonated brine baths finished.
	4/12/14†	90	106	21	43.4	+	-19	
	4/15/14†	106	120	22	26.0	+	-21	
	4/22/14†	106	116	28	23.3	49.9 : 49.9	-10	
419†	11/30/13	100	114	30	+	+	-8	Mitral obstruction.
	12/ 9/13	96	—	24	+	+	-18	Digitalis begun.
	1/10/14	92	98	37	+	+	11	

In Case 15 the cardiac efficiency factor was above 35 per cent. at all observations except one. The second phase, however, was above 40 per cent. at all observations except five. When the C. S. : C. W. ratio could be worked out it was on the side of C. S. seven times and on the side of C. W. once. The cardiac overload was above 50 per cent. four times and below 50 per cent. eight times.

In Case 127 the cardiac efficiency factor was never much above or below the normal ratio, from 25 per cent. to 35 per cent. The second phase was below 40 per cent. at three out of five observations. The C. S. factor was above the C. W. at two observations at which the ratio could be worked out, and the two were equal at the other observation. There was no overload at two observations and at the other three the overload was insignificant.

In Case 129 the cardiac efficiency factor was high at three out of four observations. The second phase was below 40 per cent. at three observations. At two observations at which the C. S. : C. W. ratio could be worked out the C. S. factor was the higher. The overload was insignificant.

In Case 176 the cardiac efficiency factor was slightly in excess. The second phase was below 40 per cent. at all observations except the last. The C. S. : C. W. ratio could be worked out at four out of six observations, and the C. S. factor was always greater. The cardiac overload was not great.

In Case 275 seven observations were made. The cardiac efficiency factor was always in the neighborhood of normal limits. The second phase was above 40 per cent. at two only. At three only could the C. S. : C. W. ratio be determined; at two of these the C. S. was greater than the C. W.; at the other the two factors were equal. The overload factor was a minus quantity at all observations except one, at which it was insignificant.

In Case 277 the cardiac efficiency factor was above the normal. The second phase was low at the observation at which it could be worked out. The C. S. : C. W. ratio was in favor of the C. S. factor. The overload was 44 per cent. at the first and 16 per cent. at the second observation.

In Case 419 the cardiac efficiency factor was about normal. The second phase and the C. S. : C. W. ratio could not be worked out. There was no overload factor except an unimportant one at the last observation (9 per cent.).

In six cases (Table 3) compensation was lost at the time the patients were first seen, but was restored after treatment so that they could resume their usual occupations. Three of the patients suffered

TABLE 3.—CASES IN WHICH COMPENSATION WAS AT FIRST LOST TO BE RESTORED SUBSEQUENTLY

No.	Date	Recurrent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
				%	%		%	
147at	10/ 2/13	84	98	24	+	+	-19	Mitral regurgitation. Decompensated. Ambulant. Compensated.
	11/ 4/13	76	92	36	+	+	8	
	1/ 8/14	84	—	46	+	+	36	Partially decompensated.
	4/ 4/14	66	74	33	+	+	0	Compensated
191	9/28/12†	68	86	45	15.7	70 : 29.8	33	Mitral regurgitation. Compensated.
	12/ 3/12*	64	70	49	+	+	46	Acute dilation.
	12/ 6/12*	60	—	40	20.0	40 : 60	17	In bed under treatment improving.
	12/17/12†	70	90	48	31.0	68.9 : 30.9	43	Up and about the house. Compensation restored.
	12/26/12†	76	96	52	29.8	74.5 : 25.3	61	After three carbonated brine baths.
	1/ 3/13†	86	96	45	36.8	75.3 : 24.8	32	After six carbonated brine baths.
	1/10/13†	68	84	49	22.0	55.8 : 43.8	48	After nine carbonated brine baths.
	1/17/13†	70	86	50	30.6	72.5 : 27.3	48	After twelve carbonated brine baths.
	2/ 6/13†	72	94	52	45.4	60.5 : 39.3	60	After eighteen carbonated brine baths.
	4/10/13†	72	84	44	45.0	64.6 : 35.2	29	Just before going to Bad Nauheim.
	9/10/13†	70	80	52	46.1	76.8 : 22.9	58	Two months after returning from Bad Nauheim.
	1/10/14†	86	114	45	+	+	29	After carbonated brine baths.
	8/12/14†	66	—	51	20.6	74.1 : 25.7	55	
291	3/24/13*	102	—	88	9.8	64.7 : 35.1	178	Aortic regurgitation. Marked decompensation.
	6/ 5/13*	112	—	58	+	+	90	Improving.
	10/ 9/13*	86	—	71	16	86 : 14	200	Compensated
	11/ 6/13†	74	80	74	20.6	82.0 : 67.7	240	
	12/16/13†	74	80	80	15.2	80.9 : 18.9	370	
355†	8/27/13	80	86	88	13.7	+	723	Aortic regurgitation. Decompensated.
	9/ 1/13	68	76	84	4.5	22.6 : 77.2	500	Some improvement.
404	10/19/13*	82	90	40	15.8	19.1 : 80.7	16	Mitral regurgitation. Partially decompensated.
	10/20/13*	84	—	34	+	+	2	Twenty-four hours rest in bed.
	10/22/13*	78	—	43	+	+	26	
	10/28/13*	82	—	50	19.3	70.9 : 28.9	50	
	11/ 6/13*	72	—	44	23.3	33.3 : 66.6	31	Patient allowed to sit up. Compensated.
	11/25/13*	70	80	46	15.6	59.1 : 40.6	36	
	12/ 4/13*	74	—	39	34.6	38.4 : 61.5	15	
	12/24/13*	84	—	42	32.0	80 : 20	23	
	1/ 8/14*	78	—	49	34.3	65.5 : 34.3	46	
	2/20/14†	70	—	45	25.9	66.6 : 33.3	21	
	3/27/14†	76	82	45	13.1	86.8 : 13.0	32	
466†	1/ 5/14	88	—	29	+	+	14	Auricular fibrillation. Decompensated.
	1/27/14	84	—	20	9†	—	-7	Compensation reestablished.

from mitral regurgitation, two from aortic regurgitation and one from auricular fibrillation.

In Case 147a the variation in the pulse-rate between the recumbent and the erect posture was 14, 16 and 8 beats at three observations. The cardiac efficiency was below 25 per cent. when he was first seen; was 36 per cent. at the second observation when compensation was good; 46 per cent. at the third observation when compensation was again partially lost, and 33 per cent. at the fourth observation, when compensation had again been restored. The second phase and the C. S.: C. W. ratio could not be determined. The cardiac overload was 19 per cent. negative at the first observation during decompensation; 8 per cent. at the second observation when compensation was restored; 36 per cent. at the third observation when compensation was again lost, and 0 at the fourth observation when compensation was restored.

In Case 191 the pulse increase between the recumbent and the erect posture was over 10 beats at eight observations, both during an attack of acute dilatation and after compensation had been restored. The cardiac efficiency factor was above 35 per cent. at every observation. The second phase rose during the course of carbonated brine baths from 15.7 per cent. to 45.0 per cent.; the C. S.: C. W. ratio fluctuated, and the overload varied, being 46 per cent. just after the acute dilatation occurred and increasing to 61 per cent. and 60 per cent. at two observations during the course of carbonated brine baths.

In Case 404 the observations on the pulse-rate in the recumbent and the erect postures were not systematically made. The cardiac efficiency factor fell from 40 per cent. to 34 per cent. after twenty-four hours in bed, but subsequently rose and was 39 per cent. or over at all the subsequent observations. The second phase formed 15.3 per cent. of the pulse-pressure at the first observation, but improved and at one time formed 34.6 per cent. of the pulse-pressure. The C. S.: C. W. ratio was at first 19.1 : 80.7 and subsequently varied, but the C. S. factor was greater than the C. W. factor at six out of eight observations. The cardiac overload was never excessive, the highest being 50 per cent. nine days before the patient was allowed to get up.

In the cases of aortic regurgitation the cardiac efficiency factor was very high both during decompensation and during compensation. The second phase was low at all times, the C. S.: C. W. ratio varied and the cardiac overload was excessive.

In the case of auricular fibrillation the cardiac efficiency factor was 39 per cent. during decompensation and 30 per cent. during compensation. The phases could not be determined during decompensation; but after compensation had been established the second phase formed 91 per cent. of the pulse-pressure. The cardiac overload factor was

TABLE 4.—CASES OF CHRONIC NEPHRITIS

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
104	2/19/12*	68	76	% 36	% 11.5	+	% 6	Chronic nephritis. Arrhythmia.
	2/29/12*	76	—	54	7.1	+	70	
	3/ 7/12*	78	—	40	+	+	47	
	3/18/12*	76	88	44	+	+	33	
	4/24/12*	60	64	57	17.5	+	83	
	5/ 8/12*	70	72	55	11.1	68.8 : 31.0	78	Arrhythmia cleared up. Feeling well.
	5/29/12*	74	98	42	10.3	+	24	
	6/26/12*	74	84	33	+	+	1	
	8/13/12*	68	78	36	13.3	+	7	
	9/15/12†	80	88	33	+	+	1	
154*	12/30/12†	82	94	29	25.5	46.4 : 53.4	—7	Return of arrhythmia.
	10/22/13†	86	92	41	26.3	+	21	
	6/24/12	74	88	41	32.5	+	21	Chronic nephritis.
	6/30/12	74	88	42	16.2	+	24	
	7/ 8/12	82	96	40	27.7	+	16	Electric light baths finished.
	7/15/12	74	78	40	19.0	+	16	
	7/22/12	72	74	38	31.7	+	13	
	8/ 5/12	—	—	42	31.2	+	25	
	9/ 2/12	—	—	38	23.8	+	12	
266†	2/28/12	74	80	40	19.6	74.1 : 25.6	17	Chronic nephritis.
	4/ 8/13	68	72	39	21.3	29.4 : 70.4	14	
	4/22/13	78	86	30	32.0	52 : 48	—7	
	6/ 2/13	72	78	39	48.4	64 : 35.8	14	
	6/30/13	90	96	38	29.5	90.4 : 9.8	10	
	7/31/13	74	—	34	25.0	82.6 : 17.2	2	Electric light baths begun.
	8/28/13	—	—	37	16.6	33.2 : 66.6	10	
	11/11/13	64	68	38	+	+	16	
	1/ 4/14	72	76	34	+	+	3	
	2/23/14	70	74	38	23.7	88.1 : 11.7	11	
431†	3/19/14	60	68	28	68.5	+	—12	Chronic nephritis.
	4/ 9/14	68	74	33	47.5	70 : 30	0	
	11/24/13	62	72	55	28.7	91.2 : 8.7	73	
	12/ 6/13	70	78	54	41.6	83.2 : 16.6	70	
	12/22/13	70	92	52	34.8	95.4 : 4.5	61	
478	2/18/14†	66	74	44	12.0	73.6 : 21.2	24	Electric light baths finished. Chronic nephritis.
	3/18/14†	78	84	52	19.7	61.9 : 38.0	59	
	3/29/14*	72	—	41	+	+	21	Attack of auricular fibrillation. In bed.
	3/30/14*	72	—	36	+	+	6	
	3/31/14*	104	—	42	+	+	24	

TABLE 4.—(Continued)

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
479	2/21/14†	100	—	% 44	% +	+	% 29	Chronic nephritis. Hyperthyroidism. In bed one week.
	2/28/14*	—	—	36	36.8	86.8 : 13.0	8	
	3/ 9/14*	--	—	42	6.9	+	22	Hospital. Hot brine baths and blanket packs.
	3/12/14*	80	—	39	15.3	+	15	
	3/16/14*	74	—	42	+	+	25	Returned from hospital.
	3/23/14*	90	—	41	31.7	+	21	
	3/28/14*	90	—	36	+	+	6	
	4/ 8/14†	96	96	44	3.6	+	31	
	4/22/14†	108	120	41	6.5	85.4 : 14.4	19	

14 per cent. during decompensation and was 7 per cent. negative after compensation had been regained.

We must not forget in the interpretation of these results that after compensation is restored these hearts are diseased. Valvular defect and the compensatory hypertrophy still make the heart an abnormal organ.

In six cases of chronic nephritis forty-eight observations were made (Table 4). The pulse-rate in the erect posture was more than ten beats above that in the recumbent posture at eight observations. The cardiac efficiency factor was above 35 per cent. at forty observations. The second phase formed less than 40 per cent. of the pulse-pressure at thirty-two. The C. S. : C. W. ratio, when it could be worked out, showed the C. S. factor in excess of the C. W. factor at fifteen observations, and a C. W. factor greater than the C. S. factor at three observations. The overload varied, but was above 50 per cent. at seven observations. The load was below the normal of 50 per cent. at three observations.

In Case 154 and Case 268, both of which showed a small overload, the symptoms were never urgent during the period of observation.

In general, it seems safe to conclude that all of these factors may be looked on as indicating to some extent the ability of the myocardium to perform its work. The variation in the pulse-rate between the recumbent and the erect posture is perhaps the least reliable.

A cardiac efficiency factor above 35 per cent., a second phase forming less than 40 per cent. of the pulse-pressure, and a cardiac overload approaching 50 per cent. or more than 50 per cent. may be looked on as pointing to myocardial insufficiency. The C. S. : C. W. ratio in many



cases cannot be worked out because the fourth point cannot be determined; but when it can be worked out a C. W. factor in excess of the C. S. factor points to serious myocardial disturbance.

I have selected nine cases from my records for the purpose of illustrating the way these factors work out on patients who clinically cannot be classed as cardiacs or as nephritics.

CASE 125.—Man, aged 54 years when first seen April 7, 1912. Chief complaint, nervousness and irritability. Physical examination revealed overweight, weak heart muscle, low blood-pressure, irritable pulse. Blood examination revealed chloro-anemia, lymphocytosis. May 3, 1913, a diagnosis of acute dilatation of the heart was made on account of an increase in the oblique diameter of cardiac dulness from 18 cm., Oct. 7, 1912, to 22 cm., muffled heart sounds and an impure systolic sound with cyanosis, palpable liver edge, a drop of the systolic blood-pressure from 100 mm. to 95 mm. and a sensation of precordial distress. In August, 1913, he had an attack of acute dyspeptic diarrhea after eating clams. In April, 1914, he had acute bronchitis.

TABLE 5.—OBSERVATIONS IN CASE 125

Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
4/ 7/12*	66	86	26	+	+	—14	
7/14/12*	60	70	35	38.8	+	4	
10/ 7/12†	66	72	30	23.3	+	—8	Clinically acute dilatation of the heart.
5/ 3/13†	72	90	30	62.0	73.3 : 27.4	—7	
5/23/13†	58	68	35	42.8	57.0 : 42.8	4	
5/27/13†	64	74	32	46.8	+	—2	
7/20/13†	56	64	31	40.7	+	—5	
9/ 1/13†	58	70	34	+	+	1	Tincture digitalis, 6 minims p. c.
4/12/14†	58	..	33	+	+	0	Digitalis stopped.

A study of the factors set forth in tabular form would seem to show that this myocardium was competent.

CASE 162.—Man, aged 37 years when first seen, July 10, 1912. The chief complaint was that a life insurance examiner had rejected him on account of pulmonary tuberculosis. Physical examination revealed healed pulmonary tuberculosis, slight hypertrophy of the heart, arrhythmia, gastrectasia, high blood-pressure. After a month spent in the Adirondack Mountains, at Fourth Lake, his symptoms had markedly improved, but the arrhythmia persisted. After taking sodium iodid for two months the arrhythmia was still present. A polygraphic tracing showed the irregularity to be due to ventricular extrasystoles. Later the arrhythmia temporarily disappeared. In March, 1913, he had an attack of spasmodic torticollis. In August, September and October, 1913, he had two attacks of acute constipation, and two attacks of acute epigastric pain. A bis-muth roentgenogram, made by Dr. M. B. Palmer, showed no organic stomach disturbance. The circulatory study would indicate a competent myocardium.

CASE 203.—Man, aged 42 years when first seen, Oct. 30, 1912. Chief complaint, cardiac arrhythmia for sixteen or seventeen years. Physical examination revealed scoliosis, arrhythmia, high blood-pressure, rapid pulse. Urine: Specific gravity 1.029 to 1.021; albumin, trace at one examination in five; a few hyaline casts twice, a few epithelial casts twice, no casts once. Eye-grounds negative after an attack of acute dyspeptic diarrhea in March, 1914 (examination made by Dr. A. C. Snell). At the time a polygraphic tracing was made the pulse was regular. The increase in heart rate between the erect and the recumbent postures, I ascribe to nervous influence. The patient had been badly scared by serious prognoses given him about his heart. The study of the circulation would indicate a competent myocardium.

TABLE 6.—OBSERVATIONS IN CASE 162

Date	Recumbent	Erect	O. E.	Second phase	O. S. : O. W.	Overload
7/10/12*	58	74	% 88	% 44.4	85.1 : 14.8	% 12
8/19/12*	66	82	39	26.8	+	15
11/19/12†	72	78	31	33.3	69.1 : 30.6	—4
12/17/12†	70	78	25	57.5	87.8 : 12.0	—15
2/19/13†	70	82	44	50	63.4 : 36.4	30
3/21/13†	66	74	21	31.8	63.6 : 36.3	—28
5/29/13†	74	90	33	37.5	62.5 : 37.5	0
10/18/13†	76	—	31	42.8	59.9 : 39.9	—4

TABLE 7.—OBSERVATIONS IN CASE 203

Date	Recumbent	Erect	O. E.	Second phase	O. S. : O. W.	Overload	Remarks
10/30/12†	72	96	% 85	% 85	+	% 5	Electric light baths and massage.
11/ 8/12†	82	88	30	26.5	77.5 : 22.4	—6	
11/22/12†	78	80	27	37.5	+	—12	
11/29/12†	76	96	26	37.8	64.8 : 35.1	—15	Electric light baths finished.
12/28/12†	74	88	27	59.5	+	—12	
2/ 8/13†	78	88	33	65.2	+	1	
3/ 8/13†	84	100	30	63.6	79.5 : 20.3	—6	Acute dyspeptic diarrhea.
5/ 2/13†	78	90	33	35.3	66.5 : 33.2	—1	
11/18/13†	88	—	27	11.9	+	—12	
3/ 4/14*	—	—	28	50.0	+	—18	
3/15/14†	90	..	27	13.3	+	—13	

CASE 233.—Man, aged 57 years. Chief complaint three persistent colds in six weeks. Physical examination revealed acute nasopharyngitis, pulmonary emphysema, palpable liver edge. The examination of the heart gave the following results: "P. M. I. fifth interspace, 10.5 cm. to the left of the midsternal line. Dulness, third rib, fifth interspace, 2.5 cm. to the right of the midsternal

line, 11 cm. to the left of the midsternal line. Oblique diameter of cardiac dulness, 17.5 cm. No murmurs. The aortic diastolic sound is louder than the pulmonary diastolic sound. The muscular quality of the systolic sound is good. Blood pressure, recumbent, Riva Rocci instrument:

First point .....	157	First phase .....	12.2 per cent.
Second point .....	150	Second phase .....	26.3 per cent.
Third point .....	135	Third phase .....	52.6 per cent.
Fourth point .....	105	Fourth phase .....	8.7 per cent.
Fifth point .....	100	C. S. : C. W. ::	78.9 : 20.9

"Pulse-pressure, 57; cardiac efficiency, 35 per cent.; cardiac load, 57 per cent.; overload, 7 per cent."

The cardiac symptoms were dyspnea and palpitation of the heart on exertion. The cardiac condition was considered at the time of the examination to be a part of an obesity; the patient was 5 feet, 9 inches tall and weighed 180 pounds, 15 ounces. The myocardium was thought to be competent. "The cardiac condition is thought to be due to the increased deposit of fat in the epicardium and not to degenerative changes in the muscle fibers."

CASE 299.—Woman, aged 40 years. Chief complaint, irregular heart. Physical examination revealed palpable liver, arrhythmia. "Heart: P. M. I., not obtainable. Dulness, third rib, fifth interspace, 3 cm. to the right of the midsternal line, 10.8 cm. to the left of the midsternal line. Oblique diameter of cardiac dulness, 16 cm. The sounds at the apex are clear. The sounds at the base are clear. The pulmonary diastolic sound is louder than the aortic diastolic sound. The muscular quality of the systolic sound is good." Blood-pressure, recumbent, Riva Rocci instrument:

First point .....	124	First phase .....	10.2 per cent.
Second point .....	119	Second phase .....	38.7 per cent.
Third point .....	100	Third phase .....	40.8 per cent.
Fourth point .....	80	Fourth phase .....	10.2 per cent.
Fifth point .....	75	C. S. : C. W. ::	79.5 : 20.4

Pulse-pressure, 49; cardiac efficiency, 39 per cent.; cardiac load, 61 per cent.; overload, 11 per cent. The urine contained neither albumin nor casts. The blood showed a polycythemia, low color index, high lymphocyte percentage (26.8 per cent.), and eosinophilia (8.4 per cent.). A polygraphic tracing gave a distinct pulsus bigeminus. The analysis of the functional tests would leave some doubt concerning the capacity of the myocardium.

CASE 309.—Woman, aged 47 years. Chief complaint, attacks of palpitation of the heart. Physical examination revealed palpable thyroid body, hypertrophy of the heart, gallop rhythm, palpable and tender liver edge, gastrectasia, high blood-pressure. The urine contained a trace of albumin and a few hyaline casts at the first examination. Gastric analysis, after Ewald test breakfast: Amount removed, 45 c.c.; free hydrochloric acid, 28; total acidity, 48; lactic acid, negative; occult blood, negative. Microscopic large amount of partly digested food not finely divided. (Examination made by Dr. C. C. Sutter.) Bismuth roentgenogram showed cowhorn type of stomach, with the greater curvature just below the umbilicus. (Examination made by Dr. M. B. Palmer.)

At the first examination there was definite evidence of disturbance of myocardial function, which improved while under treatment directed toward the dilated stomach. After the patient had omitted her treatment for about ten days the evidence of myocardial disturbance returned.

CASE 327.—Man, aged 45 years. Chief complaint pain in right side of chest. Physical examination revealed palpable liver edge, low blood-pressure, slow pulse. Urine, no albumin, one hyaline cast seen. Increase in pulse-rate between the recumbent and the erect posture, 10 beats; cardiac efficiency within normal limits; second phase below normal; impossible to obtain C. S. : C. W. ratio.

No overload. It is possible that the low second phase and the impossibility of working out the C. S. : C. W. ratio on account of the absence of the fourth point may point to myocardial weakness; but there was no clinical evidence of it.

CASE 405.—Man, aged 49 years. This patient had been refused the renewal of a life-insurance policy because his systolic blood-pressure was high (154 mm.). Physical examination showed a slight increase in the oblique diameter of cardiac dulness (17 cm.), palpable liver edge, slow pulse and an increase of twenty beats between the recumbent and the upright posture. Urine examination. Specific gravity, 1.030. No albumin, no casts. The second phase, 12.7 per cent. and the C. S. : C. W. ratio of 32.7 to 67.2 in favor of myocardial weakness are balanced by a cardiac efficiency of 35 per cent. and an overload of only 5 per cent.

TABLE 8.—OBSERVATIONS IN SIX CASES

No.	Date	Sex	Age	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
2038*	12/23/12	M	57	88	94	35	26.3	78.9 : 20.9	7	Fat heart.
2264	3/17/13	F	40	54	—	39	38.7	79.5 : 20.4	15	Hyperthyroidism
	11/11/13	..	..	—	—	38	51.0	+	11	
409*	4/22/13	F	47	100	—	41	35.0	64.7 : 35.1	21	Gastrocnasias.
	5/22/13	..	..	84	114	31	31.8	49.9 : 49.9	-4	
	6/20/13	..	..	86	—	32	44.0	60 : 40	-22	
	6/23/13	..	..	86	—	32	36.3	73.6 : 26.4	-2	
	7/22/13	..	..	84	100	32	21.7	43.4 : 56.4	-2	
	9/30/13	..	..	90	—	39	10.3	+	14	
2271	8/14/13	M	45	56	66	28	24.1	+	-14	No definite organic lesion.
405*	10/23/13	M	49	66	86	35	12.7	32.7 : 67.2	5	Hypertrophy of the heart.
416*	11/ 3/13	M	54	100	114	37	18.6	74.5 : 25.3	9	Electric light bath begun.
	11/20/13	..	..	72	—	40	26.7	78.1 : 25.8	16	
	12/10/13	..	..	72	81	45	30.5	50.6 : 40.2	34	Electric light bath finished.

CASE 409.—Man, aged 54 years. Chief complaint, abdominal pain. Physical examination revealed slight exophthalmos, enlarged thyroid body, beginning pulmonary emphysema, increased area of cardiac dulness, palpable liver edge, high blood-pressure, and rapid pulse. The patient complained of right-sided abdominal pain, which was relieved by a cathartic, and some dyspnea and palpitation of the heart on exertion, which he ascribed to his weight. Although he was apparently in perfect health, the physical examination showed definite but early changes in thyroid body, heart, lungs and liver. He weighed 203½ pounds, an excess of 26 pounds for his height, 5 feet, 11½ inches. The urine had a specific gravity of 1.011 and 1.012. Neither albumin nor glucose was present. There was a slight excess of indican. The microscope showed pus, round epithelium and phosphates.

The cardiac efficiency factor and the second phase would point to some myocardial deficiency, although the C. S. : C. W. ratio and the overload factor would not indicate such weakness. A course of electric light baths was followed by subjective improvement: that is, while he was not complaining before the baths were taken, he felt better after they had been finished and then realized that he had not been quite up to the mark. The cardiac efficiency

factor, the second phase, the C. S. : C. W. ratio and the overload then all pointed to myocardial defect. Three months later the urine had a specific gravity of from 1.026 to 1.028 and contained glucose. After two weeks on a low carbohydrate diet the total quantity of urine was 2,470 c.c.; specific gravity, 1.012; there was a trace of albumin by the Tsuchiya method; no glucose. Six weeks later the total quantity was 2,087 c.c.; specific gravity, 1.016; neither albumin nor glucose; no excess of indican.

#### CONCLUSIONS

It appears to me legitimate, from the study of the cases herein reported, to conclude that all four of these factors have some value in determining the efficiency of the myocardium. I am inclined to think at present that the cardiac efficiency factor of Tigerstedt, and the percentage of the pulse pressure formed by the second phase, are the most important. A cardiac efficiency factor of 40 per cent. or over would seem to point out distinct myocardial inefficiency. A second phase of 30 per cent. or under would seem to indicate the same condition.

The C. S. : C. W. ratio is less important, I think, because it so often cannot be determined; and again, because a small second phase is very frequently made up by a large third phase. On the other hand, a C. S. : C. W. ratio in which the C. W. factor is greater than the C. S. factor is indicative of disturbance of the myocardium, functional if not organic. I am inclined to think at present that the overload factor of Stone is indicative more of peripheral resistance than of myocardial weakness. A cardiac load below 50 per cent., as determined by this method, giving a negative overload may have some significance; but it will require further study to determine its nature.

## THE THERAPEUTIC ACTION OF IODIN\*

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Though iodine in the form of inorganic iodides or as organic compounds has been used for years, and is one of the most important drugs in the Pharmacopeia, little is known concerning its action in the body. This lack of knowledge applies particularly to its effect in causing the absorption of necrotic material such as is found in gummas.

The results obtained with the iodides have been variously ascribed to their influence in the general metabolism of the body; to their supposed action in causing a fall in blood-pressure; to a change in the viscosity of the blood; to a lymphocytosis; to an increase in the activity of the lymphatics, and to the oxidizing properties of the nascent iodine.

Binz<sup>1</sup> and Hinz<sup>2</sup> believed its action to be due to the oxidizing properties of the nascent iodine, which, according to Hinz, renders the blood-vessels more permeable and makes the leukocytes more active. Romberg<sup>3</sup> suggests that its action may be due to some change in the blood, and Müller and Inada<sup>4</sup> state that this change consists in an alteration of the viscosity. Determann,<sup>5</sup> however, denies that there is a change in the viscosity of the blood following the administration of iodides.

Various authors have ascribed the action of iodine to its property of causing a fall in blood-pressure, but Stockman and Charteris<sup>6</sup> state that there is no fall in blood-pressure when iodides are given. Lehn-dorf,<sup>7</sup> however, in a recent paper states that iodides do cause a fall of the blood-pressure, and believes that the lowered blood-pressure aids healing by permitting a better circulation of blood through the diseased area.

Much work has been done on the absorption, distribution and excretion of iodine; we shall, however, refer only briefly to this. All who have investigated the subject have found that the inorganic

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1. Binz, C.: *Arch. f. exper. Path. u. Pharmacol.*, 1894, xxxiv, 185.

2. Hinz: *Virchows Arch. f. path. Anat.*, 1899, clv, 44.

3. Romberg, E.: *Verhandl. d. Cong. f. inn. Med.*, 1904, xxi, 60.

4. Müller, O., and Inada, R.: *Deutsch. med. Wchnschr.*, 1904, xxx, 1751.

5. Determann: *Deutsch. med. Wchnschr.*, 1908, xxxiv, 871.

6. Stockman, R., and Charteris, F.: *Brit. Med. Jour.*, 1901, ii, 1520.

7. Lehn-dorf, A.: *Arch. f. exper. Path. u. Pharmacol.*, 1914, lxxvi, 224.



iodids are absorbed very rapidly, and in the main are excreted as inorganic compounds, while the organic compounds, especially those in which the iodine is combined with fatty acids, as in iodipin, are absorbed and excreted more slowly. According to Winternitz,<sup>8</sup> iodipin is absorbed from the intestinal tract as iodized fatty acids, and by oxidation of these the iodine is split off and is excreted principally in the form of inorganic iodids. Wells<sup>9</sup> concludes from his work that when iodipin is injected into the subcutaneous tissues it is carried in the blood chiefly as inorganic iodids. McLean<sup>10</sup> made a study of the distribution of iodine in the body of rabbits which had received several doses of potassium iodid, and found that the lipid fractions of the tissues contained 32 per cent. and the water-soluble fraction 67 per cent. of the iodine. The extracted protein contained no iodine. The older view that iodine combines with the proteins of the body has been disproved by McLean and other observers. We believe we are justified in assuming that a large part of the iodine combines with the lipids, as the work of McLean and Winternitz indicates that such organic compounds, whether given as such or formed in the body, are in turn readily oxidized, and the iodine excreted chiefly as inorganic compounds. Bröking<sup>11</sup> has shown that iodine administered as iodized fats or fatty acids is not excreted so rapidly as when given in the form of potassium iodid. This is to be expected, as absorption would be less rapid, and new compounds must be formed before it can be excreted, whereas potassium iodid is more readily absorbed and excreted as such.

Reference books on pharmacology and therapeutics afford but little information on the action of iodine. Forschheimer<sup>12</sup> states that iodine stimulates the activity of the lymphatics and increases the energy of the nutritive processes, and thus promotes the absorption of disease products. Schmiedeberg<sup>13</sup> states that iodine does not exert a specific action on any organ, but causes a change in metabolism and in nutritive processes in general.

In the present work we have confined our investigations of the action of iodine to its influence on the antitrypsin of the blood and tissues, as we believe that the antitrypsin is the most important factor in preventing the resolution of necrotic tissues such as are found in infarcts, and in the caseous areas in syphilis and tuberculosis.

8. Winternitz, H.: München. med. Wchnschr., 1903, i, 1241.

9. Wells, H.: Ztschr. f. physiol. Chem., 1905, lxx, 412.

10. McLean, F. C.: Organic Iodin Preparations, Their Pharmacology and Therapeutic Value, THE ARCHIVES INT. MED., November, 1912, p. 505.

11. Bröking, E.: Ztschr. f. exper. Path. u. Pharmakol., 1911, viii, 125.

12. Forschheimer, F.: Therapie Int. Dis., 1913, ii, 404.

13. Schmiedeberg, O.: Grundriss d. Pharmakologie, 1913, Ed. 7, p. 449.

## ANTITRYPSIN

In a recent publication<sup>14</sup> we reported that the ferment-inhibiting action of serum is due to the presence of compounds of the unsaturated fatty acids. The ease with which they can be extracted by chloroform or ether indicates that they are either free acids, or that they are combined with lipoids. The influence of chloroform on the antitrypsin of serum and the rapidity with which it acts is shown in Chart 1. In this experiment two volumes of chloroform were added to fresh serum and the mixture was placed in the incubator for one hour. During this time it was shaken thoroughly at short intervals. At fifteen-minute intervals some of the serum was removed and tested for its ferment-inhibiting properties. In separating the serum from the chloroform it is necessary to centrifuge at high speed for about five to ten minutes.

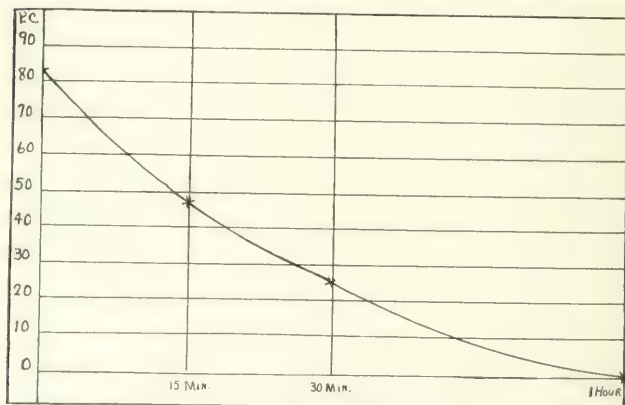


Chart 1.—Rate of removal of serum antitrypsin by chloroform extraction at 37 C. (98.6 F.).

and then to filter several times through coarse filter-paper until the serum is quite clear and all the chloroform evaporated. This experiment demonstrates that the ferment-inhibiting action of the serum is almost wholly lost after sixty minutes' incubation with chloroform.

That the inhibiting action is due to fatty acids is shown by the following experiment, the results of which are shown in Chart 2.

Ether was added to fresh dog-serum, and the mixture was allowed to stand at room temperature for two days. The ether was then removed, evaporated to dryness and the substance remaining saponified

14. Jobling, J., and Petersen, W.: *Jour. Exper. Med.*, 1914, xix, 459.

by means of sodium alcoholate. After evaporating to dryness, the soaps were dissolved in water, the acids liberated in the usual manner, taken up in ether and resaponified. These soaps and some of the untreated serum were then tested to find out their ferment-inhibiting action.

The chart shows that the soaps prepared from the ether extract cause nearly as much inhibition as the untreated serum. Subsequent experiments showed that the chloroform and ether extracts lost their ferment-inhibiting action if they were first treated with iodine, which indicates that the active agents were the unsaturated fatty acids.

The demonstration that the antitryptic action of the blood and of tuberculous caseous matter is due to the presence of unsaturated fatty acids suggested to us the possibility that the action of iodine in the body

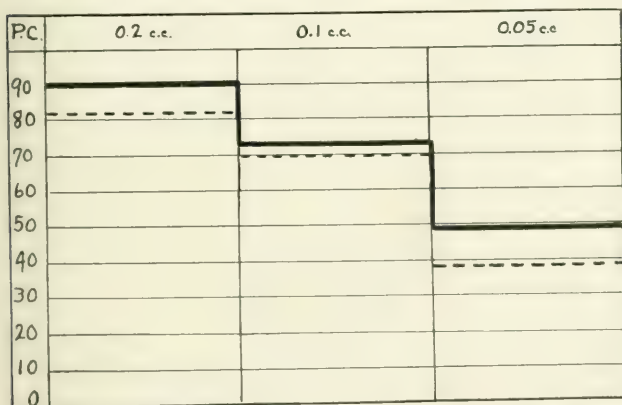


Chart 2.—Antitryptic effect of saponified ether extract of normal serum. Solid line, inhibition of normal serum; broken line, inhibition of saponified extract.

may be due to a combination with the fatty acids, thus causing a neutralization of the activity of these substances as ferment-inhibiting agents. If this supposition proved true, the neutralization of the activity of these agents should lower the antienzyme strength or the blood-tissues in general and permit the removal of dead tissues by autolysis.

The next experiment was made to determine the influence of potassium iodide on the antitrypsin of guinea-pig serum.

Fresh guinea-pig serum was mixed with potassium iodide in the proportion of 0.2 gm. of the iodide to 1 c.c. of the serum, and the mix-

ture placed in the incubator over night. Some of the untreated serum was used as a control. Chart 3 shows the results of this experiment.

The chart shows the great decrease in antitryptic strength of the serum after treatment with potassium iodid. Similar results were obtained when the serum was treated with hydrogen dioxid. The foregoing observations led us to study the antitryptic strength of the serum of patients to whom iodids were being given. It seemed probable, especially from the results obtained by McLean, that some of the iodine would combine with the unsaturated fatty acids of the body, and as a result lower the antitryptic strength of the serum and of the tissues in general. This decrease in antitrypsin would permit the ferments normally present in the necrotic areas to become active, and thus hasten autolysis.

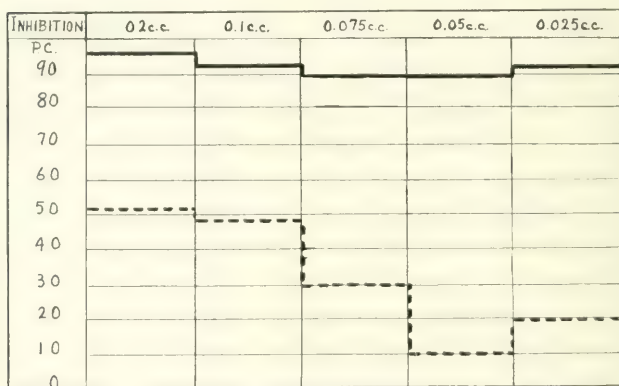


Chart 3.—Effect of potassium iodid on antitrypsin of guinea-pig serum. Solid line, normal serum; broken line, normal serum with potassium iodid incubated over night.

We are greatly indebted to Drs. J. Fordyce, W. McMurty and C. Sharpe for furnishing us with the clinical material used in this study, and also for regulating the dosage of iodids and determining the clinical condition of the patients while the work was progressing. Thirteen cases were studied, eleven of which were syphilitics. In each instance the blood was tested before iodids were given. The second test was made when the patient was receiving about 100 grains a day, and the third when he had reached the limit of tolerance. We were unable to carry out this plan in all cases, as the patients did not always follow directions.

In making the tests the trypsin was mixed with the various dilutions of serum and incubated thirty minutes. Two c.c. of a 1 per cent. casein solution was then added to each tube, and the mixtures were incubated one hour. The contents of the tubes were then acidified with a mixture containing 10 per cent. glacial acetic acid and 20 per cent. sodium chlorid and the tubes placed in boiling water for from five to ten minutes. The mixtures were then filtered through kaolin, and non-coagulable nitrogen was determined by the method recommended by Folin and Denis.<sup>15</sup> The results are given in percentage of total control digestion. The trypsin used in this work was prepared according to the method described in a previous paper,<sup>16</sup> and made into solution when required.

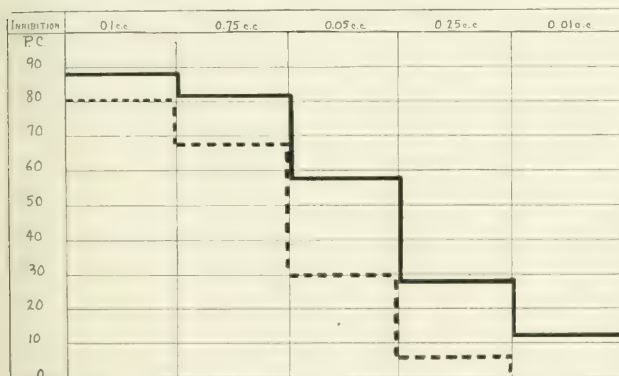


Chart 4.—Average of human cases on potassium iodid (110 gr.).

Chart 4 gives the average of the antitryptic strength of the serums of the thirteen cases before and after using iodids. The black line represents the strength of the serums before iodids were administered, and the dotted line the average strength of the serums when the patients were taking about 110 grains a day. The action of the iodids is best seen in the dilutions beginning with 0.05 c.c. of serum, though some effect is observed in the more concentrated solutions.

This series of cases is not large, but sufficiently so to show that iodids administered to human beings cause a very considerable reduction in the antitryptic activity of the blood. The difference is not so evident when larger amounts of serum are used, as here there is an

15. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1911-12, xi, 527.

16. Jobling, J., and Petersen, W.: *Jour. Exper. Med.*, 1914, xix, 239.

excess of the enzyme-inhibiting agent over that necessary to neutralize the amount of trypsin used; but in great dilutions the difference is very obvious.

It is of interest to note that in the two cases of iodism the anti-ferment was much higher than it had been during the course of treatment. This increase in the antitrypsin may be due to the failure of the iodine to combine with the unsaturated fatty acids, or to an increase of lipoids following the destruction and disintegration of cells as a result of the toxic action of the iodine. It is probably due to the latter factor. It is possible that when large doses of iodids are given there may be localized areas in which the anti-ferments are completely neutralized; with a consequent destruction of cells by the ferments present and a liberation of lipoids. Thus an increase in antitrypsin is found in almost every case in which a protein intoxication causing cellular injury with mobilization of lipoids is induced experimentally, as after anaphylactic shock, after burns, after serotoxin and anaphylatoxin injection. The iodine may also combine with and neutralize the protective substances in the cell wall and thus permit the ferments to act on them. This may partially explain the toxic action of iodine.

We have recently shown<sup>17</sup> that serum deprived of its antitrypsin becomes toxic for the species from which it is obtained. If guinea-pig serum is shaken thoroughly with two volumes of chloroform and then placed in the incubator for one hour, it becomes so toxic that 2 or 3 c.c. injected intravenously will kill a guinea-pig weighing from 250 to 300 gm. If the mixture of serum and chloroform is permitted to remain in the incubator twenty-four hours, 0.3 c.c. will frequently kill a guinea-pig of this weight. The toxicity of serum treated in this manner is due to the fact that the chloroform removes the antitrypsin, and when this occurs, the ferments, which are normally present, act on the unprotected serum proteins and produce the toxins. Autolysis occurs to a very slight degree during the first hour in the incubator, but after twenty-four hours there is a considerable increase in non-coagulable nitrogen. Up to a certain point the toxicity increases in proportion to the degree of autolysis, but it then decreases rapidly, owing to further cleavage of the toxic substances. Similar results may be obtained with any agent which absorbs the antitrypsin. Thus we have found that kaolin, agar, certain toxins and bacteria act in the same manner, though to a less degree. The antitryptic action of the serum may be destroyed without removing the lipoids. Certain oxidizing agents, such as iodine, saturate the unsaturated carbon bonds of the fatty acids, and in this way destroy their antitryptic action, and render the serums toxic. In our study of these toxins we found that the

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17. Jobling, J., and Petersen, W.: *Jour. Exper. Med.*, 1914, xix, 480.



toxicity of the serums treated by the different methods depended on the degree to which the antitrypsin had been removed. Autolysis of the serum also depends on this factor.

If the action of the iodine in causing absorption of necrotic material is due to the general lowering of the antitrypsin, large doses should cause an increase in the nitrogen output owing to the increase of proteolysis. The results of a number of experiments with dogs indicate that the iodids do increase the nitrogen output, but these experiments are not sufficiently advanced to enable us to report on them at this time.

#### TUBERCULOSIS

There is a general impression among clinicians that iodids are harmful in tuberculosis, as they promote the spread of the infection by causing a softening of the tubercles, and also interfere with connective-tissue formation. On the other hand, L. Bondreau<sup>18</sup> regards iodine as a specific in tuberculosis. He begins treatment with small amounts of the tincture (the French tincture contains 8.5 per cent. of iodine in 95 per cent. alcohol), and increases the dose to 100 drops a day. He states that some of the patients pushed the doses themselves to 200 or 300 drops a day, and one patient took 400 drops a day without the slightest inconvenience.

Loeb and Michaud<sup>19</sup> found that when iodine compounds were injected into the body tuberculous areas took up more iodine than the other tissues. They observed that a tuberculous rabbit's eye contained about twice the amount of iodine present in the normal one, and that caseous lymph-glands of guinea-pigs contained more iodine than any of the normal organs. Wells and Hedenberg<sup>20</sup> repeated the work of Loeb and Michaud, but in addition made experiments to determine the power of necrotic tissue in general to take up and hold iodine. The authors found that tuberculous lymph-glands do take up relatively more iodine from the blood than from the liver, spleen and other glands of the same animal. When the caseous material was abundant enough to permit of separation from the rest of the gland substance, it was found to contain more iodine than did the non-caseous portion. An important part of their work was the demonstration that iodine was taken up equally well by necrotic tissues and exudates produced experimentally. They conclude that the large amount of iodine present in necrotic tissues, whether tuberculous or otherwise, is dependent on

18. Bondreau, L.: *Jour. de méd. de Bordeaux*, 1914, lxxxv, 1.

19. Loeb, O., and Michaud: *Biochem. Ztschr.*, 1907, iii, 301.

20. Wells, H., and Hedenberg, O.: *Jour. Infect. Dis.*, 1912, xi, 349.

purely physical conditions, and not on a chemical attraction or physical absorption.<sup>21</sup>

Since the reports of Mosetig and Moorhof,<sup>22</sup> iodine in the form of iodoform has been used extensively in the treatment of local tuberculous conditions. Bruns and Nauwerck<sup>23</sup> found that the walls of abscesses treated in this manner were invaded by leukocytes, but they ascribed the disappearance of tubercle bacilli in the inflated tissues to the germicidal action of the iodoform. Heyn and Rovsig<sup>24</sup> and others, however, showed that iodoform has no germicidal action on tubercle bacilli. In 1904 Heile<sup>25</sup> demonstrated the presence of proteolytic ferments in the pus of tuberculous abscesses treated with iodoform, and ascribed the curative action of the iodoform to the accumulation of leukocytes. Weil<sup>26</sup> injected iodoform-glycerin mixtures subcutaneously into both healthy and tuberculous individuals in order to study their influence on the blood. Immediately following the injection there was an increase in the polynuclear cells and a decrease in the number of lymphocytes, but this was soon followed by an increase in the lymphocytes and a decrease in the polynuclears. Most of the investigators believe that the active component of the iodoform is the iodine, and as it is known that the administration of iodine causes an increase in the number of lymphocytes in the blood, Gianasso<sup>27</sup> and others ascribe its action to these cells. According to Bartel and Neuman,<sup>28</sup> the lymphocytes contain substances which neutralize the toxins of the tubercle bacilli, and Bergell<sup>29</sup> believes that this action of the lymphocytes is due to their containing lipase which acts on the neutral fat of the tubercle bacilli. Rothschild<sup>30</sup> believes that iodine stimulates phagocytosis as he found that a much larger number of the tubercle bacilli in the sputum of tuberculous patients receiving iodids were intracellular.

In our work<sup>31</sup> on the antiferments contained in tubercle bacilli and in tuberculous caseous material, we found that the enzyme inhibiting

21. In a recent paper Lewis and Krauss (*Jour. Biol. Chem.*, 1914, xviii, 313) have demonstrated that tuberculous tissue from animals which were never under iodine treatment may contain very appreciable amounts of iodine, thus throwing some doubt on the conclusions reached by Loeb and Michaud and by Wells and Hedenberg.

22. Mosetig and Moorhof: *Wien. med. Wchnschr.*, 1880, xxx, 1174.

23. Bruns, P., and Nauwerck, C.: *Beitr. z. klin. Chir.*, 1887, iii, 133.

24. Heyn, C., and Rovsig, T.: *Fortschr. d. Med.*, 1887, v, 258.

25. Heile: *Ztschr. f. klin. Med.*, 1904, lv, 508.

26. Weil, W.: *Ztschr. f. Chemotherap.*, 1913, Orig., i, 412.

27. Gianasso: Referred to in *München. med. Wchnschr.*, 1905, lii, 1990.

28. Bartel, J., and Neuman, W.: *Centralbl. f. Bakteriöl.*, 1905-1906, Orig., xl, 723.

29. Bergell: *München. med. Wchnschr.*, 1910, lvii, 1683.

30. Rothschild, W.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 404.

31. Jobling, J., and Petersen, W.: *Jour. Exper. Med.*, 1914, xix, 251; *ibid.*, 1914, xix, 383.

action was due to the unsaturated fatty acid radicles of the lipoids. At first we believed that this action was due entirely to the soaps of the unsaturated fatty acids, but subsequent work showed that a large portion of the enzyme-inhibiting agents could be removed by extracting with chloroform. The substances contained in the chloroform extracts are not active as antienzymes when suspended in salt solution, as they are insoluble; but the sodium soaps prepared from these acids are active, and we found that their activity was in proportion to the degree of their unsaturation.

In our study of soaps as enzyme-inhibiting agents<sup>10</sup> we found that certain unsaturated fatty acids in the form of soaps were very active as antiferments, but that this action was lost if the acids were first saturated with iodine. These experiments were repeated with the chloroform extracts of tuberculous caseous material and with unextracted caseous material, with the result that the soaps prepared from the chloroform extracts became inactive, and the caseous matter which, previous to treatment with iodine, had not been acted on by trypsin, became readily attacked. The loss of antienzyme action cannot be attributed to any activating influence on trypsin, as iodine inhibits the action of this ferment.

Thus we have definite evidence of the action of the iodids on tuberculous tissue, and the explanation of the well-known clinical observation that iodids cause tubercle bacilli to appear in the sputum of patients with pulmonary tuberculosis, though they were previously absent. When iodids are taken into the tissues a portion of the iodine is liberated and combines with the unsaturated carbon atoms of the fatty acids. As soon as this occurs in necrotic tissue to a degree sufficient to lower or remove the antiferment action, autolysis ensues, as in most instances ferments are present. That the inorganic iodids diffuse readily throughout caseous matter and are thus in a position to furnish the iodine has been shown by Loeb and Michaud, and Wells and Hedenberg.

Tubercles and caseous areas may be present in the lung, but unless they open into the air passages tubercle bacilli may be absent in the sputum. If iodids are now given, the caseous matter begins to soften, and is more likely to rupture into the bronchi, and the bacilli then discharged in the sputum. A somewhat similar explanation may be advanced to explain the softening and rupture of caseous areas, as in lymph-glands, when they are secondarily invaded by streptococci, staphylococci, etc. With the invasion of the infecting organism there is an increase of the blood-supply and an infiltration with polymorphonuclear cells; the increased blood-supply tends to dilute and wash out the excess antiferment, and the ferments liberated from the pus-

cells, with that already present, overcome the antiferment remaining, and softening occurs.

The sudden discharge of the softened caseous material into the bronchi as a result of the action of the iodine would also explain the occurrence of hemorrhages, as it would leave unsupported any blood-vessels traversing the mass whose walls had been involved in the tuberculous process to a degree that would render them unable to withstand the blood-pressure without some outside support. We must bear in mind the possibility and, in fact, probability, that with the softening and absorption of these caseous areas, the tubercle bacilli may be disseminated. The action of the iodids in causing a general reduction in the antiferments of the serum must also be remembered; this reduction in the serum antitrypsin would aid in bringing about the softening and removal of the caseous material.

#### SYPHILIS

Clinical experience teaches us that in the tertiary stage of syphilis iodine is almost a specific in bringing about the amelioration of symptoms and the disappearance of lesions, and yet little is known concerning the means by which these results are obtained. In reviewing the literature it was found that literally hundreds of articles had been written on the action of iodine in syphilis, but not one gave a rational explanation.

In order to arrive at some understanding concerning the action of iodine in syphilis two points must be considered: First, Does it destroy the infecting organism? Or, second, does it merely bring about resolution of the process, and leave the infecting organism to produce similar lesions?

Authorities on this subject are unanimous in the belief that iodids are not curative in the sense that they prevent the return of the lesions; this can be accomplished only when the iodids are combined with some other form of treatment. Tomaszewski<sup>32</sup> found that the administration of iodine does not prevent the development of experimental syphilis in monkeys and rabbits; neither has it a curative action; but iodized animals recovered quickly when given mercury. That iodine does penetrate into syphilitic tissues has been shown by O. Loeb.<sup>33</sup> This author made quantitative determinations of the amount of iodine in the blood and lymph-glands of syphilitic patients who had received large doses of sodium iodide. He found that the unsoftened lymph-glands contained 3.3 times and the softened glands 6.2 times the

32. Tomaszewski: *Deutsch. med. Wchnschr.*, 1910, xxxvi, 653.

33. Loeb, O.: *Arch. f. exper. Path. u. Pharmacol.*, 1912, lix, 108.

amount of iodine present in the blood. He states that most of the iodine was present as an organic compound which was insoluble in alcohol.

Wells criticizes the technic used by Loeb, and states that he always obtained larger amounts of iodine in the blood. In reply to the criticism of Wells and Hedenberg, Loeb<sup>34</sup> states that iodine is not present in syphilitic tissues merely as the result of diffusion, but that it exists as a true chemical combination with the constituents of the tissues.

As experimental work and clinical observations have demonstrated that the iodides do not destroy the infecting organism, we must assume that the results obtained are due to the power the iodides possess of causing resolution of the lesions present. That this actually occurs will be attested to by every clinician of experience.

Owing to its scarcity we have not been able to examine material from gummas, and so we are unable to state positively that the anti-enzymes present are similar to those found in tuberculous caseous matter; but it is probable that the same agents are active here as in those anemic infarcts in which autolysis does not occur. If this assumption is correct, it is not difficult to explain why large gummas rapidly disappear when the patient is brought under the influence of iodides. It is due to the fact that the unsaturated fatty acid radicals which inhibit autolysis have become saturated with iodine. As soon as this occurs, the ferments which are present, or which may be brought in, become active, autolysis takes place and the necrotic tissue is absorbed. Here, also, the local action of the ferments is made less difficult by the reduction of the antienzyme in the circulating blood. It must be borne in mind that the iodides are not remarkably effective in the earlier stages of syphilis when necrosis of tissue is not so evident.

If the foregoing interpretation of the action of iodine is correct, it gives the clinician a rational idea of what he is accomplishing when he gives iodides to a patient in the tertiary stage of syphilis. According to this view, iodine neutralizes the action of the agents which prevent solution and absorption of necrotic tissue, and at the same time lays bare to the action of the real germicidal agent the infecting organism which previously had been protected by the necrotic tissue. With the exposure of the infecting organism, such agents as mercury and salvarsan would be much more effective.

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34. Loeb, O.: *Therap. Monatsch.*, 1913, p. 178.

CASE 1.—B. S. Luetic. Positive Wassermann; no lesions.

TABLE 1.—INHIBITION IN CASE 1

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/ 9/14	0	80	79	46	19	5
5/ 6/14	34	88	79	60	0	0
5/14/14	120	75	80	19	0	0

Treatment was commenced with 10 drops of a saturated solution three times a day, and the patient ordered to increase 1 drop with each succeeding dose.

The differences are very slight, if any, when large amounts of serum are used, but with greater dilution the influence of the iodids is obvious.

CASE 2.—S. S. Luetic. Perforating ulcer of palate. Improved under treatment.

TABLE 2.—INHIBITION IN CASE 2

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/ 9/14	0	85	73	48	25	5
5/ 7/14	102	86	86	33	25	0
5/14/14	120	81	44	5	0	0

The treatment ordered was the same as in the preceding case. The patient continued taking for two weeks the same dose with which she had begun; it was then increased gradually and the day the second test was made she was taking 102 drops.

CASE 3.—A. M. Luetic. Tertiary stage. No symptoms.

TABLE 3.—INHIBITION IN CASE 3

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/25/14	0	90	80	63	30	17
4/20/14	88	70	56	25	17	0
5/ 6/14	102	60	30	0	0	0

The patient began with the usual amount, and increased it 1 drop each dose.



CASE 4.—S. Luetic. Tertiary stage. Positive Wassermann; no symptoms.

TABLE 4.—INHIBITION IN CASE 4

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/25/14	0	92	86	38	26	26
4/14/14	80	88	80	38	20	5
4/21/14	101	88	85	75	30	20
4/29/14	120	80	56	30	5	0
5/13/14	180	92	85	50	30	0

The treatment ordered was the same as in the preceding cases. At the time the last specimen of blood was taken the patient showed symptoms of iodism with well-marked rash. It is interesting to note that two cases showed iodism, and in both the antitryptic strength of the serum was as high as, if not higher, than in untreated cases.

CASE 5.—N. M. Non-syphilitic.

TABLE 5.—INHIBITION IN CASE 5

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/25/14	0	89	89	69	17	5
5/20/14	?	83	63	38	0	0
5/26/14	45	75	80	56	25	0

The patient took her medicine irregularly. The amount taken at the time the second test was made is not known; but the results indicate that she was taking more than when the third test was made.

CASE 6.—J. P. Secondary stage. No symptoms.

TABLE 6.—INHIBITION IN CASE 6

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/25/14	0	90	90	90	33	25
4/14/14	40	90	92	70	30	20
4/21/14	84	88	88	Lost	33	30
4/29/14	100	88	80	75	19	19
5/13/14	145	92	88	48	5	0

The usual treatment was given.

CASE 7.—S. F. Luetic. Positive Wassermann. Psoriasis-like lesion.

TABLE 7.—INHIBITION IN CASE 7

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/14/14	0	90	90	80	26	19
4/25/14	96	81	80	56	19	5
5/ 6/14	114	83	69	40	19	5
5/11/14	168	81	88	52	5	0
5/23/14	200	86	70	63	0	0

The treatment ordered was the same as in the preceding cases.

CASE 8.—G. H. Luetic. Tertiary stage. Skin lesions on the hands.

TABLE 8.—INHIBITION IN CASE 8

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/14/14	0	89	88	50	25	20
5/ 6/14	70	81	80	40	5	0
5/25/14	100	88	78	80	60	0

The usual treatment was given. At the time the last test was made the patient presented evidences of iodism, with a well-marked rash. Here again the antitryptic strength of the serum is increased.

CASE 9.—J. McD. Luetic. Secondary stage.

TABLE 9.—INHIBITION IN CASE 9

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/30/14	0	90	90	84	75	25
5/ 6/14	100	85	85	52	25	0

The same treatment was instituted.

CASE 10.—J. C. Luetic. Tertiary stage. Aphasia.

TABLE 10.—INHIBITION IN CASE 10

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
5/ 1/14	0	94	71	44	26	0
5/28/14	90	75	68	25	0	0

The patient received the same treatment.

CASE 11.—J. D. Non-syphilitic.

TABLE 11.—INHIBITION IN CASE 11

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/ 6/14	0	89	70	56	17	5
5/25/14	?	85	80	76	Lost	0
5/29/14	54	87	80	Lost	25	0

The patient did not return to the clinic until about six weeks after his first visit, and he took no medicine during the greater part of this time. Treatment was started again on his second visit.

CASE 12.—T. A. Luetic. Tertiary stage; no symptoms.

TABLE 12.—INHIBITION IN CASE 12

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/29/14	0	81	78	38	20	0
5/13/14	...	83	81	38	Lost	0
5/23/14	125	85	85	77	20	0

Treatment commenced April 29, 1914, with 10 mm. potassium iodid three times a day, and patient increased the dose at irregular intervals. May 26, 1914, patient was taking 125 mm.

CASE 13.—E. W. Luetic. Secondary stage. Positive Wassermann; no symptoms.

TABLE 13.—INHIBITION IN CASE 13

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/ 6/14	0	90	88	56	28	5
4/27/14	0	87	90	69	40	5
5/16/14	126	75	52	5	0	0

The patient continued taking the same quantity two weeks, and then discontinued it altogether until May 27, when she was started on 15 drops three times a day.

# OBSERVATIONS ON RENAL FUNCTION IN ACUTE EXPERIMENTAL UNILATERAL NEPHRITIS \*

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The study of renal function during the past few years has occupied considerable attention in both clinical and experimental laboratories. A number of different tests have been advocated by different observers, but so far no attempt has been made, in experimental surgery, to compare a variety of these tests on the same animal at the same time. This paper describes experiments which were made to establish an acute unilateral nephritis in dogs, and records the studies on renal function in this condition to determine which of the tests used most commonly in the surgical clinic are of greatest practical value in the diagnosis of one-sided lesions of varying severity.

An experimental one-sided nephritis has already been produced. In 1883, Ribbert<sup>1</sup> excised the medulla of one kidney in rabbits in his experiments on renal physiology. Boyd<sup>2</sup> and Oppenheimer<sup>3</sup> confirmed this method of producing a unilateral lesion by using the same technic. Oppenheimer's work is of especial interest in regard to functional studies on nephritis. By removing the cortex of one kidney, he found that the secretion of urine on that side stopped. But when the medulla was removed, there was an increased output of urine from the affected kidney which contained more sodium chlorid and had a lower freezing-point than the urine from the normal side. Yet the glycosuria resulting from subcutaneous injections of phloridzin was diminished. This, he considered, afforded evidence in favor of tubular resorption. Schlayer's<sup>4</sup> method for producing unilateral lesions consisted of the injection of epinephrin into various points of the renal parenchyma. As a result, he obtained a contracted kidney. Hirsch and Maschke<sup>5</sup>

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\* From the Laboratory of Surgical Research, Harvard Medical School, and the Medical Clinic of the Peter Bent Brigham Hospital.

1. Ribbert: Ueber Resorption von Wasser in der Marksubstanz der Niere, Virchow's Arch. f. path. Anat., 1883, xciii, 169.

2. Boyd: Some Experiments on the Functions of the Medulla of the Kidney. Jour. Physiol., 1902, xxviii, 76.

3. Oppenheimer: Experimentelle Untersuchungen über die Nierentätigkeit und ihre Beziehung zur funktionellen Diagnostik, Verhandl. d. deutsch. Gesellschaft. f. Urol., 1909, ii, 289.

4. Schlayer: Ueber künstliche Erzeugung von Schrumpfnieren, München. med. Wehnschr., 1909, lvi, 687.

5. Hirsch and Maschke: Experimentelle Untersuchungen über Nephritis, Berl. klin. Wehnschr., 1912, xlix, 145.

introduced the actual cautery into different parts of one kidney and obtained foci of scar tissue on that side. Brewer<sup>6</sup> caused pyelonephritis by the injection of pathogenic bacteria into the proximal segment of the ligated ureter, and Stewart<sup>7</sup> made a similar picture by the implantation of the ureter into the wall of the intestine. These various experiments, however, were designed to produce a chronic nephritis or depended on infection or on the introduction of artificial factors which would render the animals unfit for further studies.

For our purposes, Ribbert's<sup>8</sup> later method, as used by Baehr,<sup>9</sup> promised more satisfactory results. Ribbert exposed the renal artery of one kidney in rabbits and injected directly into it a solution of iodine which was perfused through the whole kidney by the arterial blood. Baehr, following this technic, injected the renal artery in the same way with iodine, croton oil, potassium chromate and uranium nitrate. The last substance produced marked unilateral glomerular lesions in rabbits, with little tubular destruction. By different degrees of dosage and by varying the length of time which the disease was allowed to run, various stages of acute, subacute or chronic one-sided nephritis were obtained. In our experiments, Baehr's method with uranium nitrate was followed with a few changes.

The introduction of ureteral catheterization into renal surgery opened up a brilliant field for the study of the urine excreted simultaneously from each kidney. By this method, the urine from one kidney could be compared with the urine from the other, and a number of different observations could be made to determine which kidney showed an abnormal function, and to what extent it was damaged compared with the other kidney. It is known that there is a certain variation in the amount of urine and solids excreted from the two kidneys over short intervals of time. But Albarran<sup>10</sup> and Kapsammer<sup>11</sup> have found that these differences diminish with the length of time of observation, and that normally, in an hour, nearly the same amount of urine and solids comes from each side.

6. Brewer: The Present State of Our Knowledge of Acute Renal Infection: With a Report of Some Animal Experiments, *Jour. Am. Med. Assn.*, 1911, lvii, 179.

7. Stewart: A Study of Ascending Infection of the Kidney Carried Out by the Method of Transplanting the Ureters into the Intestines, *Univ. Penn. Med. Bull.*, 1911, xxiii, 233.

8. Ribbert: Untersuchungen über die normale und pathologische Physiologie und Anatomie der Niere, *Bibliotheca Medica*, 1896, Part C, No. 4, p. 1.

9. Baehr: Ueber experimentelle Glomerulonephritis (Ein Beitrag zur Lehre der Schrumpfnieren), *Beitr. z. path. Anat. u. z. allg. Path.*, 1913, lv, 545.

10. Albarran: Recherches sur le fonctionnement normal comparé des deux reins, *Ann. d. mal. d. org. genito-urin.*, 1904, xxii, 81.

11. Kapsammer: Ueber Ureterenkatheterismus und funktionelle Nierendiagnostik, *Wien. klin. Wchnschr.*, 1903, xvi, 1417.



Certain physical, chemical and excretory properties of the urine from the two kidneys have been compared to estimate differences in renal function of the two organs under pathological conditions. Von Korányi<sup>12</sup> introduced the determination of the freezing-point of urine as an index for the functional capacity of the two kidneys. In general, he found that the concentration of the urine was less as the severity of the disease increased. Many subsequent observers have applied this method as a test for function in unilateral disease. The results obtained from it have disagreed. The bulk of evidence shows that the freezing-point of urine determines which kidney is functioning to best advantage, but that this test is by no means quantitatively accurate.

Turner<sup>13</sup> made observations on the electrical conductivity of urine under various conditions. He discovered that its electrical resistance in ohms was inversely proportional to its sodium chlorid concentration, and believed that this test, on account of its relative simplicity and the small amount of urine required in performing it, would be valuable in surgery as a means of studying the function of the individual kidney. Loewenhardt<sup>14</sup> confirmed these results by showing that under normal conditions the electrical resistance of the urine from each kidney was nearly the same, but when the function of the two kidneys varied, marked differences in electrical conductivity of the separated urines were found. A powerful advantage for this test, he declared, lay in the fact that since small amounts of urine were needed, the length of time for ureteral catheterization could be materially shortened. These findings, however, have not been accepted by many observers. Gottstein<sup>15</sup> objects to the test after careful review of the literature and from his own experience. Since electrical conductivity does not deal with the number of molecules in solution, but merely with the number of ions, it offers no information as to the total concentrative powers of the kidney, and tells but little more in regard to the degree of renal injury than a specific gravity determination.

The excretion of sodium chlorid, nitrogen or urea from the two sides has been compared in suspected unilateral disease. The amount of nitrogen or urea put out has given the most accurate information in regard to the degree of disease. While Albarran found in normal indi-

12. Von Korányi: Physiologische und klinische Untersuchungen über der osmotischen Druck thierischen Flüssigkeiten, *Ztschr. f. klin. Med.*, 1897, xxxiii, 1; *ibid.*, 1898, xxxiv, 1.

13. Turner: The Electrical Conductivity of the Blood and Urine in Health and in Disease, and as a Test of the Functional Efficiency of the Kidney, *Edinburgh Med. Jour.*, 1907, N. S., xxi, 318.

14. Loewenhardt: Weitere Ergebnisse der Bestimmung der elektrischen Leitfähigkeit des Harnes, *Deutsch. Gesellsch. f. Urol.*, 1909, ii, 281.

15. Gottstein: Der heutige Stand der funktionellen Nierendiagnostik, *Ergebn. d. Chir. u. Orthopädie*, 1911, ii, 417.

viduals that the actual amount of urea from the two kidneys was nearly the same over a given interval, Barringer<sup>16</sup> showed that in disease its total excretion varied, diminishing in almost direct proportion to the degree of injury found in one or the other organ. Many other writers have confirmed this observation.

Of the substances found in the urine under normal conditions, Wohlgemuth<sup>17</sup> has advocated the estimation of diastase as a test for the function of the two kidneys. He believes that this determination affords a simple means for estimating differences in function of the two kidneys when one is diseased, and that the amount of ferment excreted varies directly with the degree of injury on the affected side. His results in bilateral nephritis have been substantiated by von Benczur,<sup>18</sup> Geyelin,<sup>19</sup> Hirata,<sup>20</sup> Marino,<sup>21</sup> Rosenthal<sup>22</sup> and Wynhausen.<sup>23</sup> Few confirmatory studies have been made with the test in surgery except by Geraghty, Rowntree and Carey.<sup>24</sup> At present the true value of this method is undetermined.

Finally, Palmer and Henderson<sup>25</sup> have found that the urinary acidity as estimated by its hydrogen ion concentration shows marked variation in different types of nephritis. It seemed possible that this test in unilateral disease might give interesting results.

16. Barringer: The Comparison of the Total Urea Excreted by Each Kidney in Surgical Diseases of These Organs; Its Value in Estimating the Functional Capacity and Pathological Changes of Kidneys, Surg., Gynec. and Obst., 1908, vii, 651.

17. Wohlgemuth: Ueber eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments, Biochem. Ztschr., 1908, ix, 1; Beitrag zum Verhalten der Diastase im Urin, *ibid.*, 1909, xxi, 432; Experimentelle Beiträge zur Prüfung der Nierenfunktion, Ztschr. f. Urol., 1911, v, 801.

18. Von Benczur: Beitrag zur klinischen Verwertbarkeit der Diastase in Blutserum und Urin, Wien. klin. Wchnschr., 1910, xxiii, 890.

19. Geyelin: A Clinical Study of Amylase in the Urine, with Special Reference to the Phenolsulphonphthalein Test, THE ARCHIVES INT. MED., 1914, xiii, 96.

20. Hirata: Beitrag zum Verhalten der Diastase im Blut und im Urin beim Kaninchen, Biochem. Ztschr., 1910, xxviii, 23.

21. Marino: Ueber die diagnostische Bedeutung der Diastaseausscheidung im Harn, Deutsch. Arch. f. klin. Med., 1911, ciii, 325.

22. Rosenthal: Zur Frage der Ausscheidung von diastatischem Ferment im Urin, Deutsch. med. Wchnschr., 1911, xxxvii, 923.

23. Wynhausen: Quantitative Diastasebestimmungen im Harn, besonders ihre Beziehung zur Nephritis und zum Diabetes mellitus, Berl. klin. Wchnschr., 1910, xlvii, 2107.

24. Geraghty, Rowntree and Carey: The Value and Limitation of Diastase, Urea and Phthalein in Estimating Renal Function in Association with Ureteral Catheterization, Ann. Surg., 1913, lviii, 800.

25. Henderson and Palmer: On the Intensity of Urinary Acidity in Normal and Pathological Conditions, Jour. Biol. Chem., 1913, xiii, 393; Clinical Studies on Acid Base Equilibrium and the Nature of Acidosis, THE ARCHIVES INT. MED., 1913, xii, 153.

Various substances have been injected into the body and their excretion in the urine followed as tests to illustrate the comparative functions of the two kidneys. Such tests in general have depended on the kidney's ability to rid itself of dyes or drugs or to produce a glycosuria from phloridzin.

Many dyes have been tried as tests for renal function, but at present two are generally accepted as being most valuable. Voelcker and Joseph<sup>26</sup> injected a solution of indigocarmine intramuscularly, noted its time of appearance in the urine, and determined by colorimetry the total amount excreted in a given interval. In general, both the time of appearance and the amount excreted varied with the severity of the existent nephritis. Their results have been confirmed by Baetzner,<sup>27</sup> Ehrich,<sup>28</sup> Roth,<sup>29</sup> and Tanaka,<sup>30</sup> who emphasized that the time of appearance, though usually important, might be misleading in certain cases; and that, therefore, the actual amount excreted was of greater significance. Gottstein considers indigocarmine the most satisfactory single test for renal function which is used.

Rowntree and Geraghty<sup>31</sup> made use of phenolsulphonephthalein as a test for renal function, showing it to be an excellent index of both unilateral and bilateral kidney disease. Their original work has been supported by many observers, among others Behrenroth and Frank,<sup>32</sup> Cabot and Young,<sup>33</sup> Deutsch<sup>34</sup> and Keyes and Stevens.<sup>35</sup>

Von Mering<sup>36</sup> discovered that a characteristic of phloridzin, following its subcutaneous injection, was the production of a glycosuria in

26. Voelcker and Joseph: Funktionelle Nierendiagnostik ohne Ureterenkatheter, München. med. Wchnschr., 1903, I, 2081.

27. Baetzner: Funktionelle Nierendiagnostik, Berl. klin. Wchnschr., 1912, Ixix, 1521.

28. Ehrich: Diagnostischer Wert der Indigokarminprobe bei chirurgischen Nierenerkrankungen, Deutsch. med. Wchnschr., 1911, xxxvii, 526.

29. Roth: Ueber die Unzulänglichkeit der Chromocystaskopie für die funktionelle Nierendiagnostik, Ztschr. f. Urol., 1911, v, 439.

30. Tanaka: Bestimmung zur Indigocarmineaktion für die funktionelle Nierendiagnostik, Ztschr. f. Urol., 1911, v, 82.

31. Rowntree and Geraghty: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein, Jour. Pharmacol. and Exper. Therap., 1910, i, 579.

32. Behrenroth and Frank: Klinische und experimentelle Untersuchungen über die Funktion der Niere mit Hilfe der Phenolsulphonephthalein Probe, Ztschr. f. exper. Path. and Therap., 1913, xiii, 72.

33. Cabot and Young: Phenolsulphonephthalein as a Test of Renal Function, Tr. Am. Assn. G.-U. Surg., 1911, vi, 136.

34. Deutsch: Funktionelle Nierenprüfung mittels Phenolsulphonephthalein, Wien. klin. Wchnschr., 1912, xxv, 1217.

35. Keyes and Stevens: A Clinical Study of Renal Function by Means of Phenolsulphonephthalein, Am. Jour. Urol., 1911, vii, 367.

36. Von Mering: Ueber künstlichen Diabetes, Centralbl. f. d. med. Wissensch., 1885, xxiii, 531.

actively functioning kidneys. Casper and Richter<sup>37</sup> made use of this fact as the basis for a test of renal function. They injected phloridzin subcutaneously, noted the appearance time of sugar in the urine coming from each kidney, and compared the total amount of sugar excreted over a given period of time. They believed that, if one kidney were diseased, it put out less sugar than the normal kidney, the discrepancy varying in proportion to the severity of the lesion. Thus the test was not only qualitative, but also quantitative. Other observers, however, have not confirmed Casper and Richter. Though this test has many adherents, it is believed that the phloridzin test alone is not of great value.

From this short review, it is seen that tests for renal function fall into two distinct groups. The first group depends on variations in the physical and chemical properties of the urine coming from each kidney. The most important of such tests are the determination of the freezing point of the urine and the comparative amounts of nitrogen, urea and diastase excreted in a known period of time. The second group of tests depends on the ability of the kidney to excrete from the blood abnormal substances which are introduced into the circulation. The most important of this group are the indigocarmin and phenolsulphone-phthalein tests. The phloridzin glycosuria test, though strictly speaking not belonging in this group, may be included for convenience.

A number of clinical observations have been made to compare certain of these tests to decide which single one is of the greatest value. Casper and Richter compared the phloridzin test with freezing-point determinations in a number of cases. The results of these tests agreed closely. When one kidney was diseased the molecular concentration of that urine was low, the glycosuria was delayed in appearance and small in amount. When no lesion existed, the concentration of the two urines was nearly the same and the time of appearance of sugar and the amount excreted from both sides were alike. Roth<sup>38</sup> made use of indigocarmin, phloridzin and freezing point determinations in a series of comparative studies. The excretion of indigocarmin and the amount of phloridzin glycosuria paralleled each other and bore a close relationship to the freezing point. All tests pointed out the diseased kidney. Yet Roth,<sup>29</sup> in a later paper, expressed the opinion that the indigocarmin test was less delicate than the other two. Unterberg<sup>39</sup> compared the excretion of sodium chlorid and urea with freezing-point

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37. Casper and Richter: *Functional Diagnosis of Kidney Disease*, 1903, P. Blakiston's Sons & Company, Philadelphia.

38. Roth: *Zur Bewertung der Indigkarminmethode für funktionelle Nieren-diagnostik*, *Verhandl. d. deutsch. Gessellsch. f. Urol.*, 1909, ii, 305.

39. Unterberg: *Der praktische Wert der funktionellen Nierenuntersuchungen bei chirurgischen Erkrankungen der Nieren*, *Ztschr. f. Urol.*, 1909, iii, 687.

determinations and with the phloridzin test. There was a parallelism between all the tests. The freezing point varied with the amount of urine obtained, but in cases of unilateral disease it was always nearer to zero on the diseased side than on the normal side. In such cases, the chlorid and urea excretions were usually diminished.

Baetzner compared the excretion of indigocarmin with the freezing point and found that as the excretion of the dye diminished, the molecular concentration of the urine was less, and that both these tests ran parallel with the degree of renal injury. Goodman and Kristeller,<sup>40</sup> and Thomas<sup>41</sup> compared the excretion of phenolsulphonephthalein with that of indigocarmin in one-sided kidney disease. The two dyes were eliminated in amounts closely parallel; the total amount of indigocarmin excreted in proportion to the amount injected was approximately one-half that of phenolsulphonephthalein excreted. Keyes and Stevens compared the excretion of phenolsulphonephthalein with that of urea from separately catheterized kidneys. The cases which justified comparison gave the same results and showed the same ratio of functional ability. Stevens<sup>42</sup> compared the phenolsulphonephthalein test with phloridzin glycosuria and with the excretion of urea. In both normal and pathological cases, these tests gave similar results. Finally, Geraghty, Rowntree and Carey compared the excretion of phenolsulphonephthalein with urea and diastase in a series of cases. They felt that the phenolsulphonephthalein test was the most significant, that diastase was of value in the majority of cases as indicating which kidney was the more diseased, and that urea estimations almost invariably corroborated the phenolsulphonephthalein findings. A patent disadvantage of the diastase test lay in the fact that dilution of the urine affected it to a more marked extent than it did the other tests—a point which Wohlgemuth has emphasized in his experiments on dogs.

Thus, on the whole, a striking parallelism appears to exist between the tests for renal function which are generally used in surgical diseases of the kidney. Although the amount of urine excreted from the two sides may vary, its molecular concentration diminishes in proportion to the severity of the disease; it contains less nitrogen, urea and diastase; the diseased kidney in proportion to its lesion is less capable of excreting indigocarmin, phenolsulphonephthalein and sugar after

40. Goodman and Kristeller: The Value of Phenolsulphonephthalein in Estimating the Functional Efficiency of the Kidneys, *Surg., Gynec. and Obst.*, 1911, xii, 56.

41. Thomas: The Quantitative Determination of Functional Renal Sufficiency by the Dubosq Colorimeter: Indigo-Carmine versus Phenolsulphonephthalein. *Am. Jour. Med. Sc.*, 1911, cxlii, 376.

42. Stevens: The Comparative Value of Modern Functional Kidney Tests, *Jour. Am. Med. Assn.*, 1914, lxii, 1544.

the injection of phloridzin. In other words, all these various tests point to the same findings. The tests for renal function used in surgery are based on the facts that a diseased kidney is incapable of excreting solids, and that the degree of impairment of this fundamental function parallels in a general way the degree of existent disease. Therefore, the important feature in the selection of a test for renal function, when the urine from the two kidneys is compared, is to choose that one which is simplest for both surgeon and patient to perform, but which is delicate enough to point out the degree of existent disease. Tests for renal function on our dogs with unilateral nephritis were undertaken to determine this point experimentally.

#### METHOD

Dogs were anesthetized with morphin and ether. In a few animals, abdominal section through the left rectus incision was made under aseptic precautions. The left kidney was freed from its capsule and its artery and vein were dissected clean by scissors and by wiping with dry gauze. Every effort was made to avoid rupture of nerve fibers. Rubber-tipped serrefines were placed separately on both vein and artery. The kidney itself was then delivered through the abdominal wound in such fashion as to expose the renal artery to best advantage without undue tension. One c.c. of distilled water which contained the desired dose of uranium nitrate was then injected into the vessel from a 2 c.c. Record syringe with a fine pointed needle, the tip of which was bent at right angles. In a few cases in which the renal artery was doubled, each branch was clamped and was injected with half the dose. In other animals, only one branch of the renal artery was injected. In a few experiments, 2 or 5 c.c. of injection fluid were used.

After the artery was injected the arterial clamp was removed for a few seconds in order to distribute the uranium through the kidney substance as diffusely as possible. The slight bleeding at the point of puncture occasioned by this procedure was readily controlled, and the kidney as a whole became engorged. The arterial clamp was replaced. After intervals of from thirty seconds to five minutes, the point of the needle was inserted into the renal vein, and 5 c.c. of blood from the kidney were aspirated into the syringe. Whatever bleeding occurred around the needle point was controlled by walling-off sponges to prevent systemic absorption of the poison. Finally both the arterial and venous clamps were removed, the kidney replaced in its normal position and the wound closed according to usual methods.

Virtually, the same technic was used in all our experiments. The only modification in our later studies was to use a lumbar incision for exposing the kidney, instead of reaching it through the peritoneum.



In this way, a smaller incision could be made, the muscles could be separated by blunt dissection without bleeding, and the kidney could be exposed and delivered into the wound through the back with slight handling. Great care was used throughout not to traumatize the kidney.

As our primary object was to produce different degrees of pathological change, the dosage of the drug varied in individual cases. The largest amount given was 1 mg. of uranium per kilogram of body weight, the smallest dose was  $\frac{1}{20}$  mg. per kilogram of body weight. Slightly less than 0.1 mg. per kilogram of body weight was found to produce a well-marked nephritis in twenty-four hours; this consequently was the dosage which was used in the majority of our experiments.

A few typical protocols with photomicrographs of the two kidneys are given to demonstrate the efficacy of the technic.

EXPERIMENT 1.—*Severe Nephritis*.—Dog 1, weight 7 kg.

March 16: Ether-morphin anesthesia. Left rectus incision. The left kidney was exposed and delivered through the wound after the renal vessels were dissected free and clamped. One mg. per kilogram body weight of uranium nitrate in 2 c.c. of distilled water was injected into the renal artery. The arterial clamp was removed and reapplied at once. After one minute the renal vein was punctured and the blood was removed by pressure and suction. The clamps were then removed from the vessels, the kidney was replaced in normal position and the wound sewn up.

March 17: Animal appeared in good condition. It was killed twenty-four hours after operation. The right kidney weighed 40 gm. and appeared normal. The left kidney weighed 65 gm. and was dark colored, except in minute areas scattered through the parenchyma which appeared necrotic. Specimens of tissue were obtained from both kidneys, fixed in Zenker's fluid and stained with eosin and methylene blue. Microscopic sections from the right kidney were normal. Sections from the left kidney showed areas of hemorrhagic necrosis in which the normal renal structure was lacking. In other parts many of the glomeruli showed necrosis of the capillary endothelium with fibrinous thrombi in the vessel walls. The tubular epithelium was lacking in certain parts. In others, it had desquamated into the lumen of the tubule, filling it with homogeneous necrotic material and serum. Numerous polymorphonuclear leukocytes were seen throughout the entire kidney structure. On the whole, the histological picture was that of an acute unilateral nephritis with necrosis of the kidney.

EXPERIMENT 2.—*Well-Marked Nephritis*.—Dog 4, weight 9 kg.

March 23: Morphin-ether anesthesia. Left rectus incision. The left kidney was exposed and delivered through the wound after the renal vessels were dissected free and clamped. The renal artery was bifurcate, so that clamps were applied to each branch. Each artery was injected with 0.4 mg. (0.9 mg. per kilogram body weight) of uranium nitrate in 0.5 c.c. of distilled water. The arterial clamps were removed and reapplied at once. After three minutes the renal vein was punctured and the blood was removed by pressure and suction. The clamps were then removed from the vessels, the kidney was replaced in normal position, and the wound was sewn up.

March 24: The animal appeared in good condition. It was killed twenty-four hours after operation. The right kidney weighed 32 gm. and appeared



Fig. 1 (Dog 1).—Right kidney. Eosin-methylene blue staining,  $\times 20$ . No lesion made out.



Fig. 2 (Dog 1).—Left kidney. Eosin-methylene blue staining,  $\times 20$ . Necrosis of glomeruli and tubules. Edema. Leukocytic infiltration.

normal. The left kidney weighed 43 gm., and was firm and of dark color. Specimens of tissue were obtained from both kidneys, fixed in Zenker's fluid and stained with hematoxylin and eosin. Microscopic sections from the right kidney were normal. Microscopic sections from the left kidney showed considerable hemorrhage. There were a few small areas of necrosis and of polymorphonuclear leukocytic infiltration. The larger part of the kidney was much less severely damaged. The glomeruli were normal. There was considerable desquamation of epithelium and effusion of serum into the lumen of the tubules, as in the previous experiment, with the formation of similar homogeneous masses, many of which contained leukocytes. There was evidence of tubular regeneration shown by large atypical epithelial cells lining some of the tubules. No mitotic figures were seen. The histological picture, therefore, was that of a moderately severe unilateral nephritis with a small amount of necrosis, but with well-marked tubular destruction.

EXPERIMENT 3.—*Mild Nephritis*.—Dog 9, weight 6.2 kg.

April 10: Ether-morphin anesthesia. Left lumbar incision. The left kidney was exposed and delivered through the wound after the renal vessels were dissected free and clamped. The renal artery was bifurcate so that clamps were applied to each branch. Each artery was injected with 0.3 mg. (0.1 mg. per kilogram body weight) of uranium nitrate in 2.5 c.c. of distilled water. The arterial clamps were removed and were reapplied at once. After two minutes the renal vein was punctured, and the blood was removed by pressure and suction. The clamps were then removed from the vessels, the kidney was replaced in normal position, and the wound was sewn up.

April 13: Following the operation, the animal was in good condition. It was killed seventy-two hours later. The right kidney weighed 14 gm. and the left 12 gm. In the gross, both kidneys appeared normal. Specimens of tissue were obtained from both kidneys, fixed with Zenker's fluid, and stained with hematoxylin and eosin. Microscopic sections from the right kidney were normal. Sections from the left kidney showed less acute changes than the two preceding. There was no evidence of exudation or hemorrhage. The glomeruli were normal. Many of the tubules were filled with homogeneous material like that previously described, and which appeared to come from desquamated epithelium. There was considerable formation of new epithelium, and mitotic figures could be found without difficulty.

These three typical protocols illustrate that it is possible to produce an experimental unilateral nephritis by the method described, causing different degrees of severity according to the amount of poison injected and according to the length of time the disease is allowed to exist. In all our experiments, except those in which insufficient dosage of uranium was given, similar lesions were obtained. In the entire series no pathological change was found in the normal kidney, and in only one observation was thrombosis of the injected renal artery found at necropsy. Thus the method appeared satisfactory for our purposes.

At varying intervals of from twenty-four hours to eighteen days after the initial operation, the dogs were anesthetized with paraldehyd in dosage of 1.7 c.c. per kilogram of body weight. The ureters were freed by lumbar incision and were catheterized separately with fine glass cannulas. The urine from the kidneys was collected in test-tubes. The rate of respiration, the carotid blood-pressure and the rate of urinary outflow were recorded on a kymographion according to usual technic.

The amount of urine required for the various functional tests which were to be studied was so large that it was necessary to stimulate the kidneys by a diuretic. The animals at the beginning of the experiment were given 200 c.c. of water by stomach-tube and 10 per cent. saline solution intravenously. The initial dose used was 20 c.c.; this was repeated often enough to maintain a constant flow of urine. It was realized that this maneuver introduced an abnormal factor into the experiment. It was constant, however, since the sodium chlorid which came to the kidneys at any time was the same on each side. Therefore, the response of the two kidneys was considered as significant as though no diuretics had been used.

After the animal was once anesthetized and catheterized, a uniform rate of urinary outflow soon became established. The subsequent observations were divided into four periods of an hour each. During the first hour, the urine from the two sides was collected and measured. Its specific gravity was obtained by weight; its total sodium chlorid and nitrogen content as well as their concentration per hundred c.c. of urine were found by Volhard's method and Kjeldahl's method; the freezing-point was determined by Beckmann's method; the diastase content by Wohlgemuth's<sup>43</sup> method; the hydrogen ion concentration by Palmer and Henderson's method.

In the second hour the phenolsulphonephthalein test was performed. Rowntree and Geraghty's original technic was used. A solution, 1 c.c. of which contained 6 mg. of the dye, was injected intramuscularly or intravenously. A small amount of alkali was added to the test-tubes which collected the urine from each kidney. The time of appearance of the dye from the two sides was observed and the total amount excreted in an hour from each kidney was estimated in Rowntree and Geraghty's modification of the Autenrieth-Königsberger colorimeter.

Prussian blue, introduced by Schroeder van der Kolk<sup>44</sup> in histology, is recognized as being one of the standard means<sup>45</sup> for staining the renal tubules. It seemed possible that the excretion of this dye might be used as a test for renal function in the same fashion that other dyes are used. A solution was made which contained 100 mg. of potassium ferrocyanid in 1 c.c. of water and was injected intravenously. A small amount of ferric chlorid and dilute hydrochloric acid were added to the test-tubes receiving the urine from the ureteral catheters. As soon as the ferrocyanid appeared in the urine, it was precipitated as a deep

43. Wohlgemuth and Noguchi: *Experimentelle Beiträge zur Diagnostik der subcutanen Pankreasverletzungen*, Berl. klin. Wchnschr., 1912, xlix, 1069.

44. Schroeder van der Kolk: Quoted by Hartung: *Das Mikroskop*, 1866, Vieweg und Sohn, Braunschweig, ii, 124.

45. *Enzyklopädie der Mikroskopischen Technik*, 1910, Urban and Schwarzenberg, Vienna, ii, 321.

blue sediment. The time of appearance of this dye from each kidney was recorded, and the total amount excreted in one hour was quantitated in the Duboscq colorimeter by turbidometry against a standard solution of the dye precipitated in the same fashion and diluted to an appropriate bulk.

The following experiment illustrates the relative accuracy with which such readings could be obtained. A standard solution was made containing 100 mg. of Prussian blue in a liter of water. Other solutions were made containing respectively 90, 80, 70, 60, 50, 40, 30, 20 and 10 mg. of the dye, and were diluted to 1 liter. The solutions were read independently by each of us against the standard. The readings in percentage, and the average reading of our two observations is given in Table 1.

TABLE 1.—READING OF VARIOUS SOLUTIONS AGAINST A STANDARD SOLUTION

	Reading 1 Per Cent.	Reading 2 Per Cent.	Average Reading Per Cent.	Error Per Cent.
100 mg. = 100 per cent. solution	95	90	92.5	2.5
90 mg. = 90 per cent. solution	80	77	78.5	1.5
80 mg. = 80 per cent. solution	69	70	69.5	0.5
70 mg. = 70 per cent. solution	57	60	58.5	1.5
60 mg. = 60 per cent. solution	52	52	52.0	2.0
50 mg. = 50 per cent. solution	42	44	43.0	3.0
40 mg. = 40 per cent. solution	30	34	32.0	2.0
30 mg. = 30 per cent. solution	24	25	24.5	4.5
20 mg. = 20 per cent. solution	*	*	*	*
10 mg. = 10 per cent. solution				

\* Too dilute to read = "traces."

Unfortunately, in urine such satisfactory readings were not obtained. In certain cases, on the addition of hydrochloric acid and ferric chlorid, a green precipitate occurred. In others, while the diluted urine appeared blue, in the colorimeter it was of a different shade than the standard, thus interfering with the reading. Hence, in several observations no quantitative readings were attempted. Instead, one urine was compared against the other to show the comparative outputs of the two sides.

During the fourth period the indigo-carmin test was made according to Voelcker and Joseph's technic. Twenty c.c. of a 0.4 per cent. solution of the dye in distilled water were injected intramuscularly or intravenously. The time of appearance of blue in the urine was noted, and the total quantity excreted in an hour was estimated colorimetrically in the Duboscq colorimeter.

Finally, a necropsy of the animal was held, and sections from each kidney were hardened in Zenker's fluid for microscopic study. To illustrate the effect of diuresis on the excretion of diastase, the determination was made in several of the experiments both before and

after the introduction of the sodium chlorid. Indigocarmin and phenolsulphonephthalein were always given in the same animal, either intramuscularly or intravenously, in order to compare their respective rates of excretion by these two forms of injection. The colorimetric estimation of indigocarmin following its intramuscular injection was usually difficult owing to its change in color. This was often obviated by intravenous administration.

The results of these experiments fall into three groups. Group 1 consists of three control animals. Group 2 consists of animals with well-marked nephritis. Group 3 consists of animals showing functional disturbances of the kidney without definite histological changes from the normal. Protocols of these various observations are given.

#### GROUP 1: CONTROL ANIMALS

EXPERIMENT 4.—Dog 11, weight 16.7 kg. Anesthetized with paraldehyd. Ureteral catheterization after double lumbar incision. Diuresis induced by 150 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy, the two kidneys were of equal weight and appeared normal. No abnormal histological changes were found.

TABLE 2.—FINDINGS IN EXPERIMENT 4

	Right Kidney	Left Kidney
Amount of urine, first hour.....	18 c.c.	14 c.c. ‡
Specific gravity .....	1.015	1.013
Sodium chlorid per 100 c.c.....	.48 gm.	.48 gm.
Total chlorid .....	86 mg.	67 mg.
Nitrogen per 100 c.c.....	.40 gm.	.35 gm.
Total nitrogen .....	72 mg.	49 mg.
Diastase* .....	16	16
Hydrogen ionization .....	8	8.7
Phenolsulphonephthalein period:†		
Amount of urine, second hour.....	23 c.c.	20 c.c.
Appearance time of dye.....	5 minutes	5 minutes
Total excretion of dye.....	22 per cent.	24 per cent.
Indigocarmin period:		
Amount of urine, third hour.....	20 c.c.	17 c.c.
Appearance time of dye.....	5 minutes	5 minutes
Total excretion of dye.....	6 per cent.	6 per cent.
Prussian blue period:		
Appearance time of dye.....	1½ minutes	1½ minutes

\*The diastase reading in this table and others represent the amount of 0.1 per cent. starch solution digested in thirty minutes by 1 c.c. of urine at 37 C. (98.6 F.).

† Phenolsulphonephthalein and indigocarmin given intramuscularly. The indigocarmin excretion was followed for thirty minutes. One specimen of Prussian blue lost.

‡ Slight loss.

EXPERIMENT 5.—Dog 20, weight 13.3 kg. Anesthetized with paraldehyd. Double lumbar incision followed by ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injection of 10 per cent. saline solution. At necropsy the two kidneys were of equal weight and appeared normal. No abnormal histological changes were found.



TABLE 3.—FINDINGS IN EXPERIMENT 5

	Right Kidney	Left Kidney
Amount of urine, first hour.....	18 c.c.	19 c.c.
Sodium chlorid per 100 c.c.....	1.3 gm.	1.4 gm.
Total chlorid.....	234 mg.	266 mg.
Nitrogen per 100 c.c.....	.54 mg.	.64 mg.
Total nitrogen.....	97 mg.	121 mg.
Diastase before diuresis.....	64.5	64.5
Diastase after diuresis.....	32	32
Freezing-point.....	—55°	—90°
Hydrogen ionization.....	5.5	5.7
Phenolsulphonephthalein period:*		
Amount of urine, second hour.....	70 c.c.	60 c.c.
Appearance time of dye.....	1 45/60 minutes	1 45/60 minutes
Total excretion of dye.....	40 per cent.	43 per cent.
Indigocarmine period:		
Amount of urine, third hour.....	55 c.c.	50 c.c.
Appearance time of dye.....	1 45/60 minutes	1 45/60 minutes
Total excretion of dye.....	14 per cent.	14 per cent.
Prussian blue period:		
Amount of urine, fourth hour.....	30 c.c.	30 c.c.
Appearance time of dye.....	1 minute	1 minute
Total excretion of dye.....	22 per cent.	20 per cent (?)

\* All dyes were given intravenously.

EXPERIMENT 6.—Dog 25, weight 7.5 kg. Anesthetized with paraldehyd. Double lumbar incision followed by ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injection of 10 per cent. saline solution. At necropsy the two kidneys were of equal weight and appeared normal. No abnormal histological changes were found.

TABLE 4.—FINDINGS IN EXPERIMENT 6

	Right Kidney	Left Kidney
Amount of urine, first hour.....	27 c.c.	21 c.c.
Specific gravity.....	1.017	1.012
Sodium chlorid per 100 c.c.....	80 gm.	.84 gm.
Total chlorid.....	216 mg.	176 mg.
Nitrogen per 100 c.c.....	.30 gm.	.39 gm.
Total nitrogen.....	81 mg.	82 mg.
Diastase before diuresis.....	32	32
Diastase after diuresis.....	15	15
Freezing-point.....	—910°	—1.03°
Hydrogen ionization.....	7.4	7.0
Phenolsulphonephthalein period:*		
Amount of urine, second hour.....	16 c.c.	16 c.c.
Appearance time of dye.....	2 minutes	2 minutes
Total excretion of dye.....	19 per cent.	15 per cent.
Indigocarmine period:		
Amount of urine, third hour.....	27 c.c.	25 c.c.
Appearance time of dye.....	2½ minutes	2½ minutes
Total excretion of dye.....	21 per cent.	20 per cent.
Prussian blue period:		
Amount of urine, fourth hour.....	35 c.c.	35 c.c.
Appearance time of dye.....	1¾ minutes	1¾ minutes
Total excretion of dye.....		†

\* All dyes were given intravenously. There was leakage of phenolsulphonephthalein at the point of injection.

† Left kidney excreted 10 per cent. more than the right kidney. Accurate estimation impossible on account of difference in color.

These three experiments show that under the conditions stated the amount of urine normally excreted from hour to hour from the two kidneys was nearly identical. There was considerable variation in both the concentration and total output of chlorid and nitrogen, and, as a result, variation in the molecular concentration as determined by the freezing-point. The amount of diastase from the two sides was the same. Dilution of urine by diuresis had a marked effect on the excretion of this ferment, as was to be expected from Wohlgemuth's and Geraghty, Rowntree and Carey's studies. The acidity of the urine showed only slight differences. The dye substances were all excreted promptly and in corresponding amounts from the two sides. As pointed out by Goodman and Kristeller and by Thomas, the total excretion of indigocarmin was approximately one-half that of phenol-sulphonephthalein. The difficulty of quantitating the excretion of potassium ferrocyanid is illustrated by the last two experiments. There is no reason to believe that the amounts excreted from the two sides were different. Yet the precipitate from one kidney was blue and from the other green. Comparative color readings, therefore, were very inaccurate.

#### GROUP 2: ANIMALS WITH WELL-MARKED NEPHRITIS

EXPERIMENT 7.—Dog 17, weight 9.6 kg.; 0.8 mg. of uranium nitrate (0.085 mg. per kilogram body weight) injected into left renal artery according to

TABLE 5.—FINDINGS IN EXPERIMENT 7

	Right Kidney	Left Kidney
Amount of urine, first hour.....	10 c.c.	15 c.c.
Specific gravity.....	1.039	1.015
Sodium chlorid per 100 c.c.....	1.6 gm.	1.1 gm.
Total chlorid.....	160 mg.	165 mg.
Nitrogen per 100 c.c.....	2.00 gm.	.42 gm.
Total nitrogen.....	200 mg.	63 mg.
Diastase before diuresis.....	400	62.5
Freezing-point.....	-3.09°	-1.00°
Hydrogen ionization.....	5.5	8.00
Phenolsulphonephthalein period:*		
Amount of urine, second hour.....	12 c.c.	61 c.c.
Appearance time of dye.....	6 minutes	5 minutes
Total excretion of dye.....	50 per cent.	30 per cent.
Indigocarmin period:		
Amount of urine, third hour.....	8 c.c.	15 c.c.
Appearance time of dye.....	†	†
Total excretion of dye.....	20 per cent.	13 per cent.
Prussian blue period:		
Amount of urine, fourth hour.....	16 c.c.	35 c.c.
Appearance time of dye.....	4 minutes	2 minutes
Total excretion of dye.....	.....	‡

\* All dyes were given intravenously. There was leakage of phenolsulphonephthalein around the point of injection, so when the color first appeared in the urine a second injection was given. Prussian blue in both urines precipitated as a green sediment which could not be read against the standard solution. The two urines, therefore, were compared against each other.

† Identical on both sides.

‡ The left kidney excreted 66 per cent. as much as the right.

method described. Forty-eight hours later anesthetized with paraldehyd. Ureters catheterized after exposure through double lumbar incision. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney was normal. The left kidney was much enlarged, firm, and dark. Microscopic sections from the right kidney, normal. Sections from the left kidney show no glomerular lesions, but marked tubular destruction.

EXPERIMENT 8.—Dog 9, weight 6.2 kg.; 0.6 mg. of uranium nitrate (0.1 mg. per kilogram body weight) injected into left renal artery according to the method described. After seventy-two hours, anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, both kidneys looked normal. Microscopic sections from the right kidney were not remarkable. Sections from the left kidney showed no glomerular lesions, but marked tubular destruction.

TABLE 6.—FINDINGS IN EXPERIMENT 8

	Right Kidney	Left Kidney
Amount of urine, first hour.....	38 c.c.	4 c.c.
Sodium chlorid per 100 c.c.....	.5 gm.	.8 gm.
Total chlorid .....	190 mg.	32 mg.
Nitrogen per 100 c.c.....	1.00 gm.	.01 gm.
Total nitrogen .....	380 mg.	4 mg.
Phenolsulphonephthalein:*		
Appearance time of dye.....	6 minutes	29 minutes
Total excretion .....	20 per cent.	Traces

\* The dye was given intramuscularly.

TABLE 7.—FINDINGS IN EXPERIMENT 9

	Right Kidney	Left Kidney
Amount of urine, first hour.....	45 c.c.	4.4 c.c.
Specific gravity .....	1.014	1.006
Sodium chlorid per 100 c.c.....	1.5 gm.	1.2 gm.
Total chlorid .....	675 mg.	52 mg.
Nitrogen per 100 c.c.....	.31 gm.	.08 gm.
Total nitrogen .....	139 mg.	3 mg.
Diastase before diuresis .....	62.5	
Diastase after diuresis .....	32	16
Freezing-point .....	-1.08°	-1.7°
Phenolsulphonephthalein period:*		
Amount of urine .....	40 c.c.	3 c.c.
Appearance time of dye.....	2 minutes	5 minutes
Total excretion of dye.....	54 per cent.	Traces

\* Dye given intravenously.

EXPERIMENT 9.—Dog 24, weight 4.2 kg.; 0.5 mg. of uranium nitrate (0.12 mg. per kilogram body weight) injected into the left renal artery according to the method described. Two and one-half weeks later the animal was anesthetized with paraldehyd and the ureters were catheterized. Diuresis was induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney weighed 24 gm. and was normal. The left kidney weighed 17 gm., was of firm consistency and pale. The cortex was narrowed, and the kidney markings were obscured. The capsule was stripped with difficulty. Sections from the right kidney were not remarkable. Sections from the left kidney showed a considerable formation

of scar tissue. Many of the glomeruli were completely destroyed and sclerosed. In parts of the kidney, however, they were less severely damaged and showed the remains of glomerular epithelium with old fibrinous thrombi in the capillaries. In areas through the kidney, no tubular epithelium was left. Here the lumen of the tubules was filled with necrotic material and serum. In other places there was evidence of tubular regeneration as shown by large atypical epithelium. Throughout the entire kidney there was considerable edema.

EXPERIMENT 10.—Dog 18, weight 11.1 kg.; 0.8 mg. of uranium nitrate (0.07 mg. per kilogram body weight) injected into the left renal artery according to the method described. Twenty-four hours later anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy the right kidney appeared normal. The left kidney was enlarged, congested, and showed numerous small areas of necrosis. Microscopic sections from the right kidney were normal. Sections from the left kidney showed a few necrotic glomeruli, others, with fibrinous thrombi in the glomerular capillaries, and others with edema and hemorrhage into the subcapsular space. The majority of the glomeruli, however, showed no lesions. The tubules throughout the entire kidney were markedly damaged.

TABLE 8.—FINDINGS IN EXPERIMENT 10

	Right Kidney	Left Kidney
Amount of urine, first hour.....	65 c.c.	4 c.c.
Specific gravity.....	1.020	1.012
Sodium chlorid per 100 c.c.....	1.5 gm.	1.00 gm.
Total chlorid.....	975 mg.	40 mg.
Nitrogen per 100 c.c.....	.70 gm.	.02 gm.
Total nitrogen.....	455 mg.	.8 mg. (?)
Diastase before diuresis.....	500	80
Diastase after diuresis.....	32	16
Freezing-point.....	-1.5°	-1.5°
Hydrogen ionization.....	8.00	8.7
Phenolsulphonephthalein period:*		
Amount of urine, second hour.....	70 c.c.	4 c.c.
Appearance time of dye.....	1½ minutes	14 minutes
Total excretion of dye.....	61 per cent.	Traces
Indigocarmine period:		
Amount of urine, third hour.....	30 c.c.	7 c.c.
Appearance time of dye.....	2 minutes	14 minutes
Total excretion of dye.....	38 per cent.	Traces
Prussian blue period:		
Amount of urine, fourth hour.....	40 c.c.	4 c.c.
Appearance time of dye.....	1¼ minutes	21 minutes
Total excretion of dye.....	50 per cent.	Traces

\* All dyes were given intravenously.

EXPERIMENT 11.—Dog 22, weight 13.8 kg.; 1.8 mg. of uranium nitrate (0.13 mg. per kilogram body weight) injected into the left renal artery according to the method described. After twenty-four hours, anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney was normal; the left kidney was enlarged, dark red in color and of firm consistency. Sections from the right kidney were normal. Sections from the left kidney showed marked hemorrhagic necrosis destroying both tubules and glomeruli.

TABLE 9.—FINDINGS IN EXPERIMENT 11

	Right Kidney	Left Kidney
Amount of urine, first hour.....	40 c.c. in 1 hr.	1.6 c.c. in 4 hrs.
Specific gravity .....	1.018	1.015
Sodium chlorid per 100 c.c.....	1.2 gm.	1.6 gm.
Total chlorid .....	480 mg.	25 mg.
Diastase before diuresis.....	32	
Diastase after diuresis .....	16	32
Freezing-point .....	-1.17°	-.62°
Hydrogen ionization .....	Acid to phthalein	Alkaline to phthalein
Phenolsulphonephthalein period:*		
Amount of urine, second hour.....	40 c.c.	
Appearance time of dye.....	1¼ minutes	None in 1 hour
Total excretion of dye.....	49 per cent.	
Indigocarmin period:		
Amount of urine, third hour.....	40 c.c.	
Appearance time of dye.....	1¼ minutes	None in 1 hour
Prussian blue period:		
Amount of urine, fourth hour.....	40 c.c.	
Appearance time of dye.....	1½ minutes	None in 1 hour
Total excretion .....	68 per cent.	

\* All dyes were given intravenously. It was impossible to determine the indigocarmin excretion quantitatively. The urine from the affected kidney contained considerable blood.

TABLE 10.—FINDINGS IN EXPERIMENT 12

	Right Kidney	Left Kidney
Amount of urine, first hour.....	35 c.c.	.4 c.c. in 4 hrs.
Specific gravity .....	1.018	1.011
Sodium chlorid per 100 c.c.....	1.2 gm.	.9 gm.
Total chlorid .....	420 mg.	Traces
Nitrogen per 100 c.c. ....	.28 gm.	Traces
Notal nitrogen .....	98 mg.	
Diastase before diuresis .....	500	
Diastase after diuresis .....	32	Not determined
Freezing-point .....	-1.60°	Nearly zero
Phenolsulphonephthalein period:*		
Amount of urine, second hour.....	50 c.c.	
Appearance time of dye.....	2½ minutes	
Total excretion of dye.....	46 per cent.	None excreted
Indigocarmin period:		
Amount of urine, third hour.....	18 c.c.	
Appearance time of dye.....	2 minutes	
Total excretion of dye.....	15 per cent.	None excreted
Prussian blue period:		
Amount of urine, fourth hour.....	80 c.c.	
Appearance time of dye.....	2½ minutes	
Total excretion of dye.....	52 per cent.	None excreted

\* All dyes were injected intravenously. The Prussian blue reading is inaccurate on account of color changes.

EXPERIMENT 12.—Dog 23, weight 10.3 kg.; 1 mg. of uranium nitrate (0.1 mg. per kilogram body weight) injected into the left renal artery according to the method described. Ninety-six hours later, anesthetized with paraldehyd, and ureters catheterized. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney was normal. The left kidney was enlarged and markedly congested. Sections from the left kidney showed areas of hemorrhagic necrosis in which

both tubules and glomeruli were destroyed. In the greater part of the kidney, the glomeruli were severely damaged. The tubules throughout were filled with cells, serum or necrotic material. The lining epithelium when present was atypical.

EXPERIMENT 13.—Dog 12, weight 11.4 kg.; 0.8 mg. of uranium nitrate (0.07 mg. per kilogram body weight) injected into the left renal artery according to the method described. After forty-eight hours, anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney was normal. The left kidney was much enlarged, dark, and contained scattered areas of necrosis. Microscopic sections from the right kidney were normal. Sections from the left kidney showed a few areas where the glomeruli and tubules were but little damaged. The greater part of the kidney, however, showed acute degenerative changes involving both glomeruli and tubules.

TABLE 11.—FINDINGS IN EXPERIMENT 13

	Right Kidney	Left Kidney
Amount of urine, first hour.....	48 c.c.	
Specific gravity .....	1.019	
Sodium chlorid per 100 c.c.....	.94 gm.	
Total chlorid .....	481 mg.	
Nitrogen per 100 c.c.....	.94 gm.	
Total nitrogen .....	481 mg.	
Diastase after diuresis .....	32	The left kidney was anuric during the entire period of observation.
Freezing-point .....	-1.65°	
Hydrogen ionization .....	8.4	
Phenolsulphonaphthalein period:*		
Appearance time of dye.....	5 minutes	
Total excretion of dye.....	38 per cent.	
Indigocarmin period:		
Appearance time of dye.....	2 minutes	
Prussian blue period:		
Appearance time of dye.....	1½ minutes	
Total excretion of dye.....	42 per cent.	

\* Phenolsulphonaphthalein and indigocarmin injected intramuscularly. Indigocarmin gave a greenish color to the urine which was impossible to estimate quantitatively.

These experiments illustrate several of the features which have been discovered in clinical studies on renal function. The amount of urine excreted from the two sides showed marked variations. In the least severe type of nephritis, more urine appeared from the diseased side than from the control kidney. As the lesion progressed the kidney became less able to excrete fluid, and finally became anuric. The specific gravity of the urine from the diseased kidney was always less than from the normal side and had no relation, therefore, to the total fluid excretion. The concentration of sodium chlorid seemed to have no definite relation to the severity of the lesion. In four experiments, it was lower in the pathological kidney's urine than in the control's, but in two cases was higher. The total excretion, however, tended to diminish with an increasing disease. The concentration and total output of nitrogen was a better index of renal function. Both diminished



strikingly in proportion to the severity of anatomical changes found in the kidney. As the disease progressed, differences in the molecular concentration of the urine increased. As a result, the freezing-point of the urine from the affected side was nearer zero.

The diastase readings are of particular interest. In the two cases in which the determinations were made before diuresis was induced, differences were found which appeared to point out differences in degree of disease. After diuresis, however, the test was of little value. In Dog 4 the diastase reading was higher on the diseased side than on the control side, and equaled the output obtained before sodium chlorid was injected. The dog was practically anuric, and had a marked hematuria. This probably accounts for the atypical finding. In the three cases tested, there was a slight change in the hydrogen ionization of the urine from the diseased side. In two cases it was marked; in one, it was no greater than in the control series. It seems warrantable to believe, however, that in unilateral nephritis the markedly diseased kidney tends to excrete a less acid urine than normal.

The total excretion of the three dye substances was much alike and depended on the severity of the lesion. Potassium ferrocyanid and phenolsulphonephthalein were excreted with nearly equal rapidity, while indigocarmin was much less completely eliminated. The first experiment illustrates that the appearance time of a dye in the urine may give misleading information. In this animal the diseased kidney put out more urine than the normal, and the dyes from the injured side came to the urine as soon as from the control side or even sooner, although the total excretion was considerably less. In the more advanced cases, the appearance time of all the dyes from the diseased side was delayed in proportion to the severity of the lesion.

Therefore, these experiments showed that with an increasingly severe nephritis, the urine from the affected side became more dilute. The excretion of nitrogen diminished in proportion to the severity of the lesion. The excretion of chlorid was more variable. Differences in the freezing-point of the compared urines showed the diseased side and, in a general way, afforded a quantitative test for the function of the two kidneys. This determination, however, was not so accurate a test for renal function as the comparative output of nitrogen or dyes.

The excretion of the three dyes which were used afforded a good index of disturbed function. Phenolsulphonephthalein was eliminated more completely and was simpler to estimate quantitatively than indigocarmin or potassium ferrocyanid. The excretion of diastase gave valuable information in regard to the degree of renal injury except when there were marked differences in the amount of urine which came from the two kidneys.

## GROUP 3: ANIMALS WITHOUT NEPHRITIS BUT WITH ABNORMAL RENAL FUNCTION

EXPERIMENT 14.—Dog 14, weight 10.5 kg.; 0.6 mg. of uranium nitrate (0.06 mg. per kilogram body weight) injected into the left renal artery according to the method described. After twenty-four hours, anesthetized with paraldehyd.

TABLE 12.—FINDINGS IN EXPERIMENT 14

	Right Kidney	Left Kidney
Amount of urine, first hour.....	20 c.c.	25 c.c.
Specific gravity .....	1.032	1.034
Sodium chlorid per 100 c.c.....	.74 gm.	.86 gm.
Total chlorid .....	148 mg.	215 mg.
Nitrogen per 100 c.c.....	.63 gm.	.50 gm.
Total nitrogen .....	126 mg.	125 mg.
Diastase after diuresis .....	62.5	32
Freezing-point .....	—1.72°	—1.56°
Hydrogen ionization .....	7.8	7.8
Phenolsulphoncphthalein period:*		
Amount of urine, second hour .....	15 c.c.	22 c.c.
Appearance time of dye.....	2½ minutes	6 minutes
Total excretion .....	15 per cent.	16 per cent.
Indigocarmin period:		
Amount of urine, third hour.....	17 c.c.	
Appearance time of dye.....	10 minutes	15 minutes
Prussian blue period:		
Amount of urine, fourth hour.....	12 c.c.	17 c.c.
Appearance time of dye.....	†	‡
Total excretion time of dye.....		

\* Phenolsulphoncphthalein and indigocarmin were given intramuscularly. It was impossible to quantitate the indigocarmin excretion.

† Slightly sooner from the right than from the left.

‡ Left kidney excreted 10 per cent. more than the right.

TABLE 13.—FINDINGS IN EXPERIMENT 15

	Right Kidney	Left Kidney
Amount of urine, first hour.....	23 c.c.	33 c.c.
Specific gravity .....	1.012	1.008
Sodium chlorid per 100 c.c.....	1.5 gm.	1.2 gm.
Total chlorid .....	345 mg.	396 mg.
Nitrogen per 100 c.c.....	.44 gm.	.32 gm.
Total nitrogen .....	101 mg.	106 mg.
Diastase after diuresis .....	24	16
Freezing-point .....	—1.45°	—1.05°
Hydrogen ionization .....	8.3	8.3
Phenolsulphoncphthalein period:*		
Amount of urine, second hour.....	50 c.c.	60 c.c.
Appearance time of dye.....	1 minute	1 minute
Total excretion of dye.....	51 per cent.	45 per cent.
Indigocarmin period:		
Amount of urine, third hour.....	14 c.c.	20 c.c.
Appearance time of dye.....	1 minute	1 minute
Total excretion of dye.....	25 per cent.	25 per cent.
Prussian blue period:		
Amount of urine, fourth hour.....	17 c.c.	18 c.c.
Appearance of dye.....	1 minute	1 minute
Total excretion of dye .....		†

\* All dyes were given intravenously.

† Left kidney excreted 10 per cent. more than the right.

Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy the two kidneys appeared normal and were of equal weight. Sections from the left kidney showed no evidence of an acute lesion.

EXPERIMENT 15.—Dog 16, weight 7.6 kg.; 1 c.c. of normal-salt solution was injected into the left renal artery according to the method described. Twenty-four hours later the animal was anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy the two kidneys appeared normal and were of equal weight. Sections from the left kidney showed no evidence of an acute lesion.

EXPERIMENT 16.—Dog 19, weight 10 kg.; 0.9 mg. of uranium nitrate (0.08 mg. per kilogram body weight) injected into the left renal artery according to the method described. There was slight leakage at the point of injection. After forty-eight hours, anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injection of 10 per cent. saline solution. At necropsy the two kidneys were of equal weight and appeared normal. Microscopic sections from the right kidney were negative. Sections from the left kidney were not remarkable except for a few foci of round-cell infiltration. There was no evidence of any acute lesion.

TABLE 14.—FINDINGS IN EXPERIMENT 16

	Right Kidney	Left Kidney
Amount of urine, first hour.....	15 c.c.	30 c.c.
Specific gravity .....	1.007	1.004
Sodium chlorid per 100 c.c.....	1.24 gm.	1.5 gm.
Total chlorid .....	186 mg.	450 mg.
Nitrogen per 100 c.c.....	.43 gm.	.27 gm.
Total nitrogen .....	64 mg.	81 mg.
Diastase before diuresis .....	64	64
Diastase after diuresis .....	8	8
Freezing-point .....	-1.63°	-1.33°
Hydrogen ionization .....	7.8	7.8
Phenolsulphonephthalein period:*		
Amount of urine, second hour.....	20 c.c.	50 c.c.
Appearance time of dye.....	1½ minutes	1½ minutes
Total excretion of dye.....	35 per cent.	38 per cent.
Indigo carmin period:		
Appearance time of dye.....	2 minutes	2 minutes
Total excretion of dye.....	24 per cent.	26 per cent.
Prussian blue period:		
Amount of urine, fourth hour.....	20 c.c.	50 c.c.
Appearance time of dye.....	1¼ minutes	1½ minutes

\* All dyes were given intravenously. It was impossible to estimate either the total or comparative output of potassium ferrocyanid on account of differences in color.

EXPERIMENT 17.—Dog 15, weight 9.6 kg.; 0.6 mg. of uranium nitrate (0.06 mg. per kilogram body weight) injected into the left renal artery according to the method described. Five days later anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy, the two kidneys were of equal weight and appeared normal. No abnormal histological changes were found.

EXPERIMENT 18.—Dog 26, weight 7.2 kg. The left kidney was exposed and handled as usual without injection of the renal artery. Twenty-four hours later the animal was anesthetized with paraldehyd and the ureters were catheterized. Diuresis was induced by 200 c.c. of water by stomach-tube and by intravenous

injections of 10 per cent. saline solution. At necropsy, the two kidneys were of equal weight and appeared normal. Nothing abnormal was found in either kidney by histological examination.

TABLE 15.—FINDINGS IN EXPERIMENT 17

	Right Kidney	Left Kidney
Amount of urine, first hour.....	16 c.c.	45 c.c.
Specific gravity .....	1.033	1.015
Sodium chlorid per 100 c.c.....	.60 gm.	1.00 gm.
Total chlorid .....	96 mg.	450 mg.
Nitrogen per 100 c.c.....	.46 gm.	.31 gm.
Total nitrogen .....	73 mg.	139 mg.
Diastase after diuresis .....	64	32
Freezing-point .....	-2.31°	-2.00°
Hydrogen ionization .....	8.0	5.5
Phenolsulphonephthalein period:*		
Amount of urine, second hour.....	15 c.c.	45 c.c.
Appearance time of dye .....	4 minutes	4½ minutes
Total excretion of dye.....	30 per cent.	35 per cent.
Indigocarmin period:		
Amount of urine, third hour.....	22 c.c.	45 c.c.
Appearance time of dye.....	†	†
Total excretion of dye.....	18 per cent.	18 per cent.
Prussian blue period:		
Amount of urine, fourth hour.....	12 c.c.	32 c.c.
Appearance time of dye.....	‡	‡
Total excretion of dye.....		

\* Phenolsulphonephthalein and indigocarmin were given intramuscularly. It was impossible to determine accurately the relative or absolute amounts of potassium ferrocyanid excreted on account of color changes.

† Identical on both sides.

‡ Slightly sooner from the right kidney than from the left. Left kidney excreted considerably more than the right.

TABLE 16.—FINDINGS IN EXPERIMENT 18

	Right Kidney	Left Kidney
Amount of urine, first hour.....	18 c.c.	65 c.c.
Specific gravity .....	1.017	1.012
Sodium chlorid per 100 c.c.....	1.6 gm.	1.3 gm.
Total chlorid .....	288 mg.	845 mg.
Nitrogen per 100 c.c.....	.62 gm.	.22 gm.
Total nitrogen .....	117 mg.	143 mg.
Diastase before diuresis .....	32	16
Diastase after diuresis.....	4	3
Freezing-point .....	-1.35°	-.85°
Hydrogen ionization .....	7.4	7.0
Phenolsulphonephthalein period:		
Amount of urine, second hour.....	16 c.c.	38 c.c.
Appearance time of dye.....	2½ minutes	2 minutes
Total excretion of dye.....	40 per cent.	42 per cent.
Indigocarmin period:		
Amount of urine, third hour.....	25 c.c.	31 c.c.
Appearance time of dye .....	1¾ minutes	1¾ minutes
Total excretion of dye.....	20 per cent.	20 per cent.
Prussian blue period:		
Amount of urine, fourth hour.....	42 c.c.	61 c.c.
Appearance time of dye .....	2 minutes	1½ minutes
Total excretion of dye.....		*

\* Left kidney excreted nearly twice as much as right. Accurate estimation impossible on account of differences in color.

The striking feature in the last series of experiments was the pronounced polyuria occurring from the side which had been manipulated. It occurred during each of the four hours of observation and so cannot be attributed to a normal variation in the amount of urine excreted. The specific gravity of the urine from the polyuric kidney was always the lower. Both the concentration of sodium chlorid and its total output varied widely. But in every instance, the total output of sodium chlorid from the abnormal side was greater than from the control side. The concentration of nitrogen from the diseased kidney was lower in every case than from the normal kidney. The total output for the period, however, was considerably higher than on the control side. In every case, the freezing-point was lower in the normal urine than in the urine from the polyuric kidney, which showed that the kidney with polyuria secreted a urine of less molecular concentration than normal. As might be expected from the previous notes, the diastase readings were insignificant. In two cases, the reaction of the urine was more acid from the diseased side than from the control. In the other cases the hydrogen ionization of the two urines was the same. As in the preceding experiments, the excretion of dyes from the two kidneys was parallel. In the case with the least polyuria, the appearance time of all the dyes from the affected kidney was delayed. In the remaining experiments, the dyes appeared in the two urines at approximately the same time. The total amount of dye excreted from the two kidneys in each instance was nearly the same. In certain of the experiments one or another dye appeared to be excreted from the diseased side in an amount above normal.

Thus, these experiments are radically different from those observations in which the kidney was definitely diseased. Here the amount of urine, nitrogen and chlorid which was excreted from the injured kidney was greater than from the control side, and the amount of dyes put out was at least normal. The explanation of these findings is uncertain. Further studies in this condition are necessary to understand its significance.

#### SUMMARY

Experiments have been undertaken to compare, on the same animal, the tests for renal function which are most commonly used in studying unilateral disease. Nephritis was produced by the injection of uranium nitrate into the renal artery of one kidney, according to the method of Ribbert and Baehr. By this procedure, one-sided lesions of varying intensity were caused.

The results of these experiments fall into two groups. One group consists of animals whose kidneys anatomically were normal yet functionally were pathological. The functional condition encountered suggested a hyperpermeability of the kidney to water, chlorid, nitrogen

and in certain instances, to various dyes. No explanation for these findings is offered.

The other group of experiments consists of animals in which a well-marked nephritis was produced. In these animals, tests for renal function were applied and gave results similar to those which have been reported in human beings.

Clinical studies have suggested that a close parallelism exists between the degree of kidney destruction and the kidney's ability to excrete various solid substances; and that all the tests most commonly used in the study of renal function give parallel results. The experiments reported demonstrate by a variety of tests for renal function made on the same animal at the same time that such a parallelism does exist, but that certain of the tests are more significant than others.

The total excretion of nitrogen from one kidney over a given period of time, as compared with its excretion from the other kidney, gives accurate information in regard to the existence and degree of disease. The comparative excretion of diastase from the two kidneys is a valuable test for renal function when the amount of urine from the two kidneys is nearly the same. This test has a striking disadvantage. Dilution of urine produces such marked differences in the diastase excretion that when the urine from the two kidneys is excreted in different amounts the observation becomes valueless. As the renal disease advances and the urine becomes more dilute, the freezing-point approaches zero. This determination, however, is not so sharp a quantitative test for renal function as the excretion of nitrogen or dye substances.

Of the two dyes commonly used, phenolsulphonephthalein is the better. It can be injected in small bulk, is excreted rapidly from the kidneys, and the amount put out can be quantitated accurately. Indigocarmin does not show changes in renal function which are not demonstrated by phenolsulphonephthalein, and has two disadvantages. It requires a considerable amount of injection fluid and its excretion is difficult to read colorimetrically. The latter objection can be obviated, in part, by intravenous administration of the dye. The excretion of potassium ferrocyanid parallels that of phenolsulphonephthalein and indigocarmin, but is more difficult to estimate colorimetrically. Hence, for practical purposes, it is of no value as a test for renal function. The reaction of the urine from a severely diseased kidney apparently tends to become less acid than that from the normal side. This variation, however, is not sufficiently marked to be used as a functional test for one-sided disease.

It appears, therefore, from the foregoing experimental observations, that renal function is best estimated by the determination of nitrogen excretion and by the phenolsulphonephthalein test.



## STUDIES IN PAROXYSMAL EDEMA\*

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Recently two cases with histories of periodic attacks of generalized edema without the usual evidence of kidney disease have been under observation in the Massachusetts General Hospital. These seem, together with certain chemical investigations on them, to be of sufficient interest to be reported.

**CASE 1.—History.** Mrs. D., aged 33, in excellent circumstances, at an early age was operated on for acute appendicitis. Since this operation a previous troublesome constipation has been more marked. In 1909, at the end of her last pregnancy, she was seriously ill with the kidney of pregnancy. During this time there appeared in the urine large amounts of albumin and casts which gradually disappeared after the birth of the child. For the past three or four years she has been engaged actively in social and philanthropic interests.

In June, 1913, the patient came to Dr. Edsall for the first time, complaining of attacks of prostration, associated with nausea, which passed off after rest. At other times she has attacks in which there is a generalized edema resulting in a gain of as much as 15 pounds in weight. The edema rapidly passes off as soon as free catharsis is established. Accompanying the edema the only symptom is an unpleasant feeling of tenseness of the skin. The attacks of edema are prone to occur when she becomes constipated, and are said to bear some relation to menstruation.

**Physical Examination.**—The physical examination is negative. Repeated examination of the urine failed to reveal casts or albumin.

**Management.**—Inability of the kidney to excrete chlorids was suspected of being the cause of the attacks of edema and in July the patient was put on a diet low in salt. Since she has been on this diet she has had no attacks similar to those previously described, except on one occasion when additional salt was given to test the functional capacity of the kidney for salt excretion. On four different occasions in October and November her daily excretion of sodium chlorid was determined and was between 2 and 3 grams. In December on two successive days she was given 6 grams additional salt with the result that on those days her twenty-four-hour amount of sodium chlorid excretion was only 0.32 gm. on the first, and 0.75 gm. on the second day. Accompanying the ingestion of the salt there was nausea and edema, which disappeared as soon as free catharsis was established. More extensive and accurate chemical studies were impossible because the patient was not in the hospital.

**CASE 2.—History.**—The second case, a Russian Jew, aged 40, was on the recommendation of Dr. J. H. Pratt, admitted to the East Medical Service of the Massachusetts General Hospital, Feb. 24, 1914, complaining of cough, dyspnea and swelling of the face, body and extremities.

**Family History.**—Not remarkable.

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*Past History.*—The patient had measles in childhood and bronchitis ten years ago; otherwise has considered himself well. He is habitually constipated. He has not had tonsillitis, rheumatism or scarlet fever and denies venereal disease. He does not use tea, coffee, alcohol or tobacco excessively. His work is selling salt fish, which requires no great exertion, but much walking.

*Present Illness.*—Six years ago he first noticed swelling of the scrotum associated with a slight dry cough, but no dyspnea, or swelling of the legs. After two weeks' rest the swelling of his testicles disappeared and the cough ceased.

A year later, five years ago, there was a return of the edema of the scrotum with edema of the legs, abdomen, chest and face, associated with some shortness of breath. A similar attack has occurred each year, and each time has passed off after a two weeks' rest.

For the past six months he has had varying degrees of edema of the face, abdomen and legs, and moderate dyspnea. During the past week both the edema and the dyspnea have increased. He has had no orthopnea, but is subject to choking attacks in which he gets blue in the face. His urine is scanty.

*Physical Examination.*—This shows a man of medium height able to lie flat in bed without discomfort, breathing noisily but not rapidly. The face is markedly edematous, the puffiness about the eyes nearly closing them. The skin, sclerae, mucosae and lymph-nodes reveal nothing abnormal. The pupils are equal, regular and react normally. The tongue, throat and tonsils are generally reddened. There is marked pyorrhea alveolaris. The heart's impulse is neither seen nor felt at the apex; the left border of cardiac dulness on percussion is 13 cm. to the left, the right border 3 cm. to the right of the midsternal line. The heart sounds are regular and of good quality. There is heard over the precordia a cardiorespiratory murmur. The pulmonic second sound is louder than the aortic and is accentuated. The pulses are of good volume and tension. The artery walls are easily palpable and distinctly thickened. Nothing is found in the lungs. There is shifting dullness in the abdomen, but no fluid wave can be made out. Neither spleen nor liver is felt, no masses or tenderness discovered. There is a marked soft edema of the abdominal wall, of the penis and scrotum and a massive brawny edema of the legs and thighs.

The Wassermann reaction on the blood is negative. The urine on repeated examinations showed no albumin or anything abnormal in the sediment.

*Clinical Course.*—He was kept in bed, given no drugs and put on a salt-low diet. The remarkable diuresis, loss of weight and diminishing edema is best appreciated by consulting the accompanying table. In five or six days he reached what may be assumed to be his normal weight. All subjective symptoms cleared rapidly with the loss of edema and he was soon up about the ward without dyspnea or any return of the edema. Dr. J. H. Pratt made daily observations on the blood-pressure and heart condition.

March 3. The apex is noted as being in the sixth space, visible and easily palpable, 14 cm. outside the midsternal line.

March 5. Orthodiagram by Dr. Holmes shows the heart shadow enlarged to the left and lying somewhat horizontal in the chest. The apex is in the sixth space, 10 cm. to the left of the median line. The right border is 8 cm. to the right of the median line. The total transverse diameter is 18 cm.

March 17. The apex impulse is visible and palpable in the fifth space, 10 cm. from the median line. Sounds are loud and clear.

The systolic blood-pressure at entrance was 150 mm. where it remained for seven days, then falling to 115 mm. where it stayed while the patient remained in the hospital. The diastolic was 115 mm. at entrance and constant for eight days, then becoming 100 mm., did not change until the patient left the hospital.

In the second case the periodicity and degree of edema without evidence of kidney disease as determined by the usual clinical examina-

tion, and a history of circulatory disturbance not of sufficient severity to explain the condition satisfactorily, suggested more careful studies of the functional activities of the kidney. Accordingly the following observations were made.

1. Urinary output and specific gravity.
2. The urinary acidity (hydrogen ion concentration) as estimated by Henderson and Palmer.<sup>1</sup>
3. Titratable acid of the urine as described by Henderson.<sup>2</sup>
4. Urinary ammonia, Folin's new method.<sup>3</sup>
5. Chlorids, Volhard's method.
6. Phenolsulphonephthalein excretion as described by Rowntree and Garaghty.<sup>4</sup>
7. Salt, lactose and potassium iodid excretion was determined as recommended by Schlayer.<sup>5</sup>

The urinary nitrogen was also determined, but as the patient's diet was not analyzed the nitrogen balance is only approximate.

#### DISCUSSION

Bohne<sup>6</sup> in 1897 first recognized reduced excretion of chlorids in cases with edema and later, in 1902, Widal<sup>7</sup> and Strauss<sup>8</sup> pointed out the important relation between edema and sodium chlorid retention in connection with therapeutic measures in these cases. So much literature on the subject has accumulated that it is impossible in a brief report of this nature to review critically the experimental and clinical facts on sodium chlorid metabolism brought to light in the various papers. Excellent reviews have been made by von Noorden,<sup>9</sup> Chris-

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1. Henderson, L. J., and Palmer, W. W.: The Intensity of Urinary Acidity in Normal and Pathological Conditions, *Jour. Biol. Chem.*, 1913, xiii, 393.

2. Henderson, L. J.: The Process of Acid Excretion, *Jour. Biol. Chem.*, 1911, ix, 403.

3. Folin, O., and MacCallum, A. B.: The Determination of Ammonia in Urine, *Jour. Biol. Chem.*, 1912, xi, 523.

4. Rowntree, L. G., and Garaghty, J. T.: An Experimental and Clinical Study of Phenolsulphonephthalein in Relation to Renal Function in Health and Disease, *THE ARCHIVES INT. MED.*, 1912, ix, 284.

5. Schlayer and Takayasu: Untersuchungen über die Funktion kranker Nieren beim Menschen, *Deutsch. Arch. f. klin. Med.*, 1910-11, ci, 333.

6. Bohne, J.: Ueber die Bedeutung der Retention von Chloriden im organismus für die Entstehung urämischer und comatöser Zustände, *Fortschr. d. Med.*, 1897, xv, 121.

7. Widal, F.: La cure de déchlorination, *Bull. méd. d. hôp.*, Paris, 1903, xx, 773, 990.

8. Strauss, H.: Zur Behandlung und Verhütung der Nierenwassersucht, *Therap. d. Gegenw.*, 1902, iv, 444; 1903, v, 193.

9. von Noorden, C.: *Metabolism and Practical Medicine*, English translation, 1907, ii, 461, Chicago.

TABLE GIVING DATA OF METABOLISM

Date	Fluid Intake	Urine, c.c.	Sp. Gr.	Total Solids	$\text{H}^+$	Acid N/10 c.c.	Ammonia N/10 c.c.	Acid + Ammonia N/10 c.c.	Acid + Ammonia	NaCl
Feb.										
25	640	900	1.022	43.5	5.1	485	716	1201	0.68	36
26	640	2,180	1.012	57.5	5.7	262	430	692	0.61	17.0
27	990	3,420	1.011	83.0	7.3	34	265	299	0.13	24.2
28	870	5,940	1.009	117.0	7.4	0	118	118	0.00	38.2
Mar. 1	1,000	4,120	1.010	90.2	7.3	41	108	149	0.38	28.4
2	1,200	2,200	1.013	63.0	7.2	66	85	151	0.78	16.0
3	985	1,580	1.020	70.0	7.0	126	85	211	1.58	9.9
4	1,455	1,700	1.016	60.0	6.9	235	143	378	1.64	9.6
5	1,500	600	1.020	26.4	5.1	352	161	416	1.54	2.4
6	1,480	1,120	1.020	31.7	5.3	415	276	691	1.30	4.5
7	1,450	840	1.024	44.4	5.3	326	300	626	1.12	2.5
8	1,500	800	1.020	35.2	5.2	326	300	626	1.00	2.2
9	1,500	1,020	1.019	42.6	5.1	344	364	708	0.95	3.8
10	1,500	900	1.019	37.6	5.0	336	356	692	0.95	4.0
11	1,500	1,050	1.018	†	...	...	...	...	...	...
12	1,380	780	1.025	43.0	5.3	300	300	600	1.00	5.9
13	1,700	720	1.024	38.0	5.3	238	288	526	0.83	8.2
14	1,500	880	1.023	44.5	5.3	300	306	606	0.98	11.8
15	1,500	1,020	1.020	44.9	5.3	420	400	820	1.05	8.2
16	1,500	880	1.017	33.0	5.3	264	238	502	1.11	6.2
17	1,500	†	.....	.....	...	...	...	...	...	...

\* Hydrogen ion concentration expressed as the

† Two grams of lactose excreted in eight hours.

logarithm of the actual value. The minus sign is  
Seven and one-half grains potassium iodid excreted in

## CASE 2 ON SALT-LOW DIET

Food Nitrogen	Total Nitrogen in Urine	Nitrogen Balance	Food, Calories	Weight, Pounds	Diet
4.8	.....	.....	.....	.....	500 c.c. milk.
7.4	7.80	- 0.4	987	.....	640 c.c. milk.
8.3	8.80	- 0.5	1,118	161½	800 c.c. milk.
5.6	8.75	- 1.8	1,028	149½	800 c.c. milk.
8.5	7.60	+ 0.6	1,141	136½	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter.
6.8	7.95	+ 1.9	1,316	128½	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter.
8.0	8.30	0.0	1,129	123	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added.
12.1	.....	.....	2,192	120¾	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added.
12.1	.....	.....	2,192	119	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
10.5	.....	.....	1,894	118	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
14.0	.....	.....	2,569	117	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
14.0	.....	.....	2,569	117½	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
14.0	.....	.....	2,569	117¾	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
14.0	.....	.....	2,569	117	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
14.0	.....	.....	2,569	117	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
14.0	.....	.....	2,569	117	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
14.7	.....	.....	2,704	116¾	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
14.7	.....	.....	2,704	118	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk. Add 50 gm. bread, 10 gm. NaCl.
14.7	.....	.....	2,704	118¼	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk. Add 50 gm. bread, 10 gm. NaCl.
14.7	.....	.....	2,704	118	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk. Add 50 gm. bread.
14.7	.....	.....	2,704	118	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk. Add 50 gm. bread.

mitted. † Phenolsulphonephthalein 90 % in two hours.  
 ty-eight hours. Non-coagulable nitrogen in the blood—40 mg. to 100 c.c. blood. (Kindness of Dr. Denis.)

tian,<sup>10</sup> Georgopulos<sup>11</sup> and Widal.<sup>12</sup> The connection between sodium chlorid and edema is well established.

The chief point of contention centers about the question whether the retention of salt is the cause or the result of water retention. Many authors, Strauss,<sup>8</sup> Widal,<sup>7</sup> Halpern,<sup>13</sup> Castaigne<sup>14</sup> and others, believe that salt retention in the tissues is primary. If saline solution be injected into normal animals and animals in which nephritis has been produced experimentally, no difference is to be found in the urine, whereas, if both animals are bled and saline solution injected soon after, the blood of the nephritic contains less salt. These experiments led Castaigne to favor the primary salt retention theory. Salt retention in certain febrile diseases as lobar pneumonia, typhoid fever, rheumatic fever, gastric carcinoma and tuberculosis is considered by Achard,<sup>15</sup> Loeper,<sup>15</sup> Laubry<sup>16</sup> and Müller<sup>17</sup> as further evidence of primary salt retention. Georgopulos<sup>11</sup> believes the kidney becomes impermeable to water so that sodium chlorid is retained to satisfy the laws governing osmotic pressure in the body. The impermeability on the part of the kidney to salt is deemed of prime importance by Widal, Strauss, Halpern, Schlayer and others. Evidence was early presented by Cohnheim and Lichtheim<sup>18</sup> that injury to the capillary walls leading to increased permeability to salt probably played an important part in salt retention. They were not able to produce edema of the subcutaneous tissues by injecting large amounts of saline solution until the tissues had been injured in some way. Magnus<sup>19</sup> confirms this view in experiments, in which he was not able to produce a general edema by injecting large amounts of salt solution until he had poisoned the

10. Christian, H. A.: *Experimental Nephritis*, Boston Med. and Surg. Jour., 1908, clviii, 416, 452.

11. Georgopulos: *Experimentelle Beiträge zur Frage Nierenwassersucht*, Ztschr. f. klin. Med., 1906, lx, 411.

12. Widal, F.: *Die Kochsalzentziehungskur in der Brightschen Krankheit*, Verhandl. d. Cong. f. inn. Med., 1909, p. 43.

13. Halpern, M.: *Beiträge zur Frage des Verhältnisses der Chlorid im Körper, ihre Beziehung zur Oedembildung und ihre Bedeutung für die Diätetik bei Nephritis*, Beitr. z. wissensch. Med. u. Chem. (Festschr. f. Salkowski), Berlin, 1905, p. 125.

14. Castaigne, J.: *Le rôle du reins dans la rétention chlorurée*, Semaine méd., 1903, xxiii, 309; 1905, xxv, 472.

15. Achard and Loeper: *Sur la rétention des chlorures dans les tissus an coeurs de certains états morbides*, Compt. rend. Soc. de biol., 1901, p. 346.

16. Achard and Laubry: *Injections salines et rétention des chlorures*, Semaine méd., 1902, xxii, 105.

17. Müller, F.: *Morbus Brightii*, Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 64.

18. Cohnheim, J., and Lichtheim, L.: *Ueber Hydrämie und hydrämisches Oedem*, Virchows Arch. f. path. Anat., 1877, lxix, 106.

19. Magnus, R.: *Ueber die Entstehung der Hautoedem bei experimentelle hydrämischer Plethora*, Arch. f. exper. Path. u. Pharm., 1899, xlii, 250.



animal with either arsenic, chloroform, chloral hydrate or ether. Müller believes there is some toxic agent which renders the capillaries more permeable to chlorids. His view is shared by Jackson and Elting.<sup>20</sup> After reviewing the many cases reported in the literature, one is impressed with the fact that any one explanation is frequently inadequate for all the various conditions encountered. In most of the cases reported there is definite kidney disease or marked circulatory disturbance. Persistent hereditary edema of the lower legs (Milroy's disease), general edema occurring in children with gastro-intestinal disturbances, angioneurotic edema and edema neonatorum need not concern us here.

Jackson and Elting<sup>20</sup> have reported a case of edema in which there was no evidence of kidney disease, but the patient had been working for years in a vitiated atmosphere due to the decomposition of linseed oil, gums, resins and hydrocarbon compounds. The history was one of gradually increasing edema until it became very marked. Examination of the heart, lungs and urine were negative. The treatment with a salt-low diet, sweating and the usual diuretics had no effect on the edema. A marked diuresis with a large increase in the sodium chlorid elimination followed the administration of potassium nitrate. As Jackson and Elting were able to find no anatomical condition to explain the edema in their case they concluded that increased permeability of the capillaries to salt due to certain toxins and the increased combining power of the tissues for chlorids could best account for the condition.

In the cases here reported there is no evidence of kidney disease as determined by the usual urinary examination. The chief points of interest in the first case are, a history of a kidney of pregnancy, recurrent attacks of generalized edema usually associated with constipation, relief from symptoms on a salt-low diet and freedom from constipation, and a marked decrease in chlorid excretion in the urine after the addition of the small amount of 6 grams of salt to the intake. There seems to be definite incompetency on the part of the kidney to excrete chlorids. Although the kidney is able to take care of 2 to 3 grams daily, any increase in the demand for sodium chlorid excretion temporarily, at least, markedly reduces this particular function. That the bowel is important in the excretion of salt in this case seems very probable. The rôle of the bowel in chlorid elimination has been studied by Javal<sup>21</sup>

20. Jackson, H. C., and Elting, A. W.: *Clinical Notes and Physicochemical Study of Salt Elimination in the Urine of an Individual with General Edema of Obscure Origin, Followed by Cure*, Albany Med. Ann., 1909, xxx, 74.

21. Javal, M. A.: *De l'élimination du chlorure de sodium par la diarrhée*, Semaine méd., 1903, xxiii, 224.

and Halpern,<sup>13</sup> who found that normally and usually in nephritis the salt excretion by bowel is insignificant, amounting to a few tenths of a gram daily; in nephritis, however, with or without diarrhea, there may be as much as 3 to 5 grams excreted in the feces daily.

The data presented in connection with the second case are interesting. Following a day's rest on a restricted diet there occurred a quite remarkable urinary crisis. During five days, February 26 to March 2, inclusive, on a total fluid intake of only 4.7 liters the urinary output was nearly 18 liters. The loss in weight was 41½ pounds, or nearly one-third of the normal weight.<sup>22</sup> The total chlorid ingestion was not more than 15 gm., while the excretion was 124 gm., or 109 gm. in excess of the intake. On February 28 the sodium chlorid excreted was over 38 gm., or 35 gm. in excess of the day's ingestion, a record which I have not seen equaled in the literature. Cases with marked urinary crises are reported. In 1905 Rolleston and Attlee<sup>23</sup> reported a case of a man aged 36 with nephritis who lost 64½ pounds in sixteen days while taking caffein citrate, gr. 7, three times a day. Rolleston and Goda,<sup>24</sup> in 1909, reported a case of nephritis in a man of 27 who lost 59 pounds in four days, the only therapy being hot air baths.

Relative to the salt metabolism in the second case the effect of the addition of salt to the diet on February 12, 13 and 14, is interesting. During these three days 30 gm. of salt with the salt in the diet, which may be estimated as 9 gm., making a total of 39 gm., were ingested. For the three days the total excretion is only 26 gm., nor is the difference to be found in the day following. It should also be noted that there was no gain in weight. That there can be chlorid retention without edema has been shown by Ambard and Beaujard.<sup>25</sup> But it seems improbable in this case. With the history of the preceding case in mind, it is interesting that during the three days of extra salt he had three to four loose dejections daily. Unfortunately, the importance of this was noticed too late to save the feces for chlorid estimations. The percentage of sodium chlorid in the urine indicates, according to Schlayer and his school, little trouble with the function of the tubules of the kidney. Through the diuresis the percentage was constant, diminishing considerably after the disappearance of the edema to a minimum of 0.28 per cent., and increasing as markedly on the addition

22. Unfortunately the patient was not weighed until he had been in the hospital two days. From his urinary output it is safe to say that his loss in weight was nearer 50 pounds than 40.

23. Rolleston, H. D., and Attlee, John: Extraordinarily Rapid Diminution of Renal Dropsy under Citrate of Caffeine, *Lancet*, London, 1905, ii, 1394.

24. Rolleston, H. D., and Goda, F. L.: A Case of Edema with Resolution by Urinary Crisis, *Brit. Med. Jour.*, 1909, i, 330.

25. Ambard, L., and Beaujard, E.: La rétention chlorurée sèche, *Semaine méd.*, 1905, xxv, 133.

of salt to a maximum of 1.34 per cent. without any increase in the urinary output.

The behavior of the acid factors are very suggestive. From a highly acid urine, 5.1, on the day of entrance it rapidly became alkaline, 7.4 (approximately the reaction of normal blood). Contrary to what might be expected, the titratable acid and ammonia were much reduced on the day of the largest amount of urine. On the first day the total acid excretion on a low diet was 1,201 c.c. as against the normal 687 c.c. on a full diet for a hydrogen ion concentration only slightly lower.<sup>26</sup> During the first few days the ratio of acid to ammonia was normal, but following the diuresis there was an increase in the acid over the ammonia, a relation which I have found to be significant in certain types of nephritis.<sup>27</sup> This low ammonia, however, persists for a few days only. Its significance in this particular case is uncertain. It has been shown that mild grades of acidosis undoubtedly exist in many cases with edema.<sup>28</sup> The significance of the peculiar acid factors in this case is not clear, but some disturbance in body reaction seems probable.

Rather more phenolsulphonephthalein, 90 per cent., was excreted in two hours than is normally the case. Baetjer,<sup>29</sup> and Pepper and Austin<sup>30</sup> have reported several cases of nephritis in which the phenol-sulphonephthalein excretion was higher than normal. Baetjer also found increased permeability to lactose with a normal potassium iodid output, a condition which he calls superpermeability of the kidney. In my case the lactose was somewhat delayed if the normal excretion of 2 grams of the substance intravenously be considered as six hours. The time of the potassium iodid output was within normal limits, forty-eight hours. In Baetjer's cases, as also in mine, the non-coagulable nitrogen in the blood was not abnormally high.

In the second case the following facts seem to me important: First, extensive generalized subcutaneous edema in the absence of any discoverable renal disease or irritation; second, mild circulatory symptoms but a distinct cardiac enlargement and a well-marked arteriosclerosis; third, a rapid disappearance of the edema on rest and diet. This evidence throws a strong suspicion on the circulatory system as playing a prominent part in causing the attacks of edema. The response of

26. Henderson, L. J., and Palmer, W. W.: The Several Factors of Acid Excretion, *Jour. Biol. Chem.*, 1914, xvii, 305.

27. Unpublished data.

28. Palmer, W. W., and Henderson, L. J.: Chemical Studies on Acid Base Equilibrium and the Nature of Acidosis, *THE ARCHIVES INT. MED.*, 1913, xii, 153.

29. Baetjer, W. A.: Superpermeability in Nephritis, *THE ARCHIVES INT. MED.*, 1913, xi, 593.

30. Pepper, O. H. P., and Austin, J. H.: Interesting Results with the Phenol-sulphonephthalein Test, *Am. Jour. Med. Sc.*, 1913, cxlv, 254.

the body to additional salt by only a moderate increase of salt in the urine, although there was a nearly normal increase in the percentage, and the associated diarrhea, suggest some renal impermeability to salt.

#### SUMMARY

The cases reported illustrate again the well-known relation between sodium chlorid and edema, and suggest a possible explanation in some cases of edema of obscure cause. The impermeability to salt on the part of the kidney is an important factor.

Attention is called to the bowel as a vehicle for the excretion of salt. This fact is important in the treatment of cases with edema of obscure origin.

In certain types of edema there may exist mild grades of acidosis which may play some rôle in the persistence of the condition.

## BOOK REVIEWS

L'ALTERNANCE DU COEUR: ÉTUDE CRITIQUE ET CLINIQUE. Par Laurent Gravier; Moniteur d'Histologie à la Faculté de Médecine de Lyon. Paris: J. N. Baillière et Fils, 1914, pp. 429.

When it is possible to publish a book of 429 pages devoted to the single symptoms of alternation, the study of the arrhythmias of the heart may be said to have reached a point of great intensity. In undertaking his task Gravier has brought together all that is known of fact and of theory on the subject. He recalls that it was Traube, so many of whose suggestions regarding the clinical pathology of the heart have borne valuable fruit, who in 1872 first devised the term and described the condition. The present insight into the subject of alternation, however, dates really from about 1900, when the studies of Mackenzie and Wenckebach began to enrich this field. The definition of the rhythm which Gravier adopts and from which there can be no substantial difference of opinion is that it represents a variation (an alternation) in the force of succeeding contractions without an alteration in their rhythm; equidistance in time is maintained among succeeding beats.

Gravier describes alternation depending on ventricular contraction, as manifested in cardiograms, in arteriograms, in phlebograms and in electrocardiograms; alternation of auricular contractions is described from the same points of view. The theories which have been advanced to explain the occurrence of alternation are stated and minutely discussed. In the last section, the etiology, prognosis, and therapy are described.

The relation of alternation of the heart to the electrocardiogram has a special interest. Alternation in the height of R- and T- waves have been described by numerous observers, but the question whether electrical alternation has the same significance as alternation in mechanical curves of arteriogram or cardiogram, and whether the two run parallel, is still much discussed. Gravier, in reviewing the field, concludes that electrical alternation is often wanting when mechanical alternation is marked, and when present may be less marked than the mechanical. On the other hand, the electrical variety may exist without the mechanical, and in still other cases, when both appear, small mechanical waves correspond to tall electrical waves, and vice versa. But the important point seems to be that alternation depends for whatever prognostic value can be assigned to it, on the mechanical curve. So far as curves showing the electrical variety do not supply information of this order, mechanical ones must be made to provide it.

Two main theories of alternation have been advanced, that of Wenckebach, who describes it as the occurrence of hyposystole affecting the ventricles as a whole; and that held among others by Hering and proposed by Gaskell, who believe it to depend on asystole of a portion of the ventricular wall. For its production the Wenckebach theory depends on the varying durations of systole and diastole, a long diastole being followed by a stronger contraction. The Gaskell-Hering theory, according to which it is believed that a portion of the ventricular muscle fails altogether to contract, depends on the idea that this portion continues in a refractory period when the rest of the ventricle is ready to beat, and a weak beat results. At the next contraction, all the muscle is again fit, and a strong beat is made. Gravier's discussion of these theories is detailed and careful. It suffices to say that after weighing the evidence, he inclines to accept the partial asystole theory of Gaskell. As to whether the occurrence depends on one of the special functions, irritability, conductivity, or contractility, authors are divided, but most agree to its being associated with a defect in the last. Gravier prefers not to commit himself on this point, and thinks it sufficient to call it a "disorder of the refractory phase."

The causes of the irregularity are found to lie in infections and cachexias and in the heart failure of the various cardiovascular diseases. As to the significance of its presence, one may say that in severe states of disease its presence is not necessarily of evil omen, but indicates a situation the interpretation of which demands caution. On the other hand, alternation may be absent, even in terminal conditions.

This study of Gravier's deserves commendation on the grounds of thoroughness, completeness, and thoughtfulness. It is written with the clearness and simplicity characteristic of French writing.

THE LIFE AND LETTERS OF NATHAN SMITH, M.B., M.D. By Emily A. Smith. With an Introduction by William H. Welch, M.D., LL.D., Price, \$2.25. New Haven: University Press, 1914.

This brief, clear and intimate study of one of the master minds of American medicine is most timely. Our medical biography is meager; Nathan Smith is one of its most attractive subjects. We are rapidly obliterating some of his creations and our methods have been so changed that his struggles will become increasingly difficult for us to understand. The work is brief, like Smith's own masterpiece, his work on typhoid fever. Documentary material was scanty, but fortunately it was telling, and the author had used it with conspicuous skill. There is in the first place the picture of the man, a heroic figure, like his younger contemporary Beaumont. His courage and resourcefulness, that were so often tried later, showed as a lad when, a militia soldier fighting Indians, he was made a captain at the age of 18. His relation to medical education, as student and teacher, illustrates some aspect of medical schools not only forgotten, but misunderstood. When he wished to study medicine there were only three schools in the young and sparsely settled country, practically devoid of means of communication. The so-called colleges and universities neglected professional education as they did for a century afterward. We can see the enthusiastic youth working hard to acquire a sufficient preliminary education to satisfy the man he had chosen as his preceptor. We have to imagine the toilsome three years of apprenticeship with the older man. Two years later the results of practice had lighted an unquenchable longing to learn from others more fortunate, and a year at Harvard medical school, then at Cambridge, followed. Then came the burning desire to found a medical school, not for a title, not for money, but in order to enable others to gain a knowledge of medicine under better conditions than he himself had had. The early struggles and disappointments at Dartmouth were probably not extraordinary, but there is something profoundly touching in the year of exile, away from his young wife, in Edinburgh and London. The beginning of the Dartmouth school and the labors there as a whole faculty, as well as physician, surgeon, obstetrician and specialist to the district, have been told by brilliant writers, but here one can learn from brief letters, as from the scanty strokes of a master etcher. We see also, besides the full and successful life, the misunderstandings, obstacles and regrets. How successful, appears from the fact that in a given period Dartmouth graduated nearly 50 per cent. more physicians than did Harvard. Then came the call to Yale, with honors, appreciation, larger opportunities, and the same strenuous life. Later came work at Bowdoin, where he began the summer course, and at Vermont. The careers of the sons, one of whom became as famous as the father, are briefly set forth. The work makes it clear that the memorials of Nathan Smith should be treasured as those of Sydenham. His virtues may be emulated even in these days of specialization. His "keen discriminating inquisitiveness," his unconquerable spirit in the face of difficulties—which indeed he overcame without thinking about that feature, will always be necessary in the study and practice of medicine. The preface by Dr. Welch illuminates the period and the work itself. The typographic and other mechanical features are attractive, and the little book should have many readers.



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## MALIGNANT SYMPATHICUS TUMOR OF THE RIGHT SUPRARENAL \*

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DES MOINES, IOWA

Through the work of A. Kohn,<sup>1</sup> Wiesel<sup>2</sup> and others, it is now definitely known that the medullary portion of the suprarenals is of nervous origin. According to Wiesel, certain cells from the neural canal become the building cells of the sympathetic system, and from them arise either chromoblasts, which accumulate in the paraganglia or wander into the suprarenals and later give rise to the chromaffinic cells, or neurocytes, which later develop into ganglion cells. Held<sup>3</sup> states that these cells may also give rise to neuroglia. Now there have been observed tumors partly composed of ganglion cells and nerve fibers, and also new growths containing chromaffinic cells. But the most interesting of all these neurogenic tumors is a very malignant form which occurs apparently only in young children, and is most often found closely associated with the suprarenals. It has long been known that malignant tumors occur in young children in the region of the kidneys, but Wright<sup>4</sup> was the first to describe them accurately and to suggest their close relation to the sympathetic system. Lately Schilder,<sup>5</sup> Landau,<sup>6</sup> and Herxheimer<sup>7</sup> have reported cases of this nature and have discussed them at length. Since these rare new

\* Submitted for publication July 29, 1914.

\* From the Pathological Institute of the German University in Prague, Prof. A. Ghon, director.

1. Kohn, A.: Das chromaffine Gewebe, *Ergebn. d. Anatomie u. Entwicklungsgesch.*, 1902, xii, 253.

2. Wiesel, J.: Beiträge zur Anatomie und Entwicklung der menschlichen Nebenniere, *Anatom. Hefte*, 1902, xix, 483.

3. Held, H.: Ueber den Bau der Neuroglia, *Leipsic*, 1903.

4. Wright, J. H.: Neurocytoma or Neuroblastoma, a Kind of Tumor not Generally Recognized, *Jour. Exper. Med.*, 1910, xii, 556.

5. Schilder, P.: Ueber das maligne Gliom des sympathischen Nervensystems, *Frankfurter Ztschr. f. Pathol.*, 1909, iii, 317.

6. Landau, M.: Die malignen Neuroblastoma des Sympathikus, *Frankfurter Ztschr. f. Pathol.*, 1912, xi, 26.

7. Herxheimer, G.: Ueber Tumoren des Nebennieren-Markes, insbesondere das Neuroblastoma sympathicum, *Beitr. z. path. Anat. u. z. allg. Path.*, 1913, lvii, 112.

growths present phases that are far from being understood at present, I wish to report an interesting instance.

#### REPORT OF CASE

*Clinical Diagnosis.*—Sarcoma of kidney; peritonitis.

*History.*—The child, aged 2 years, entered the Kaiser Franz Josef Spital (Professor Bayer's service), April 5, 1914, with the complaint that a swelling of the abdomen had been noted for four weeks. During that time there had been fever. The child had lost flesh, had been peevish, and toward the last had had frequent stools and urination. The father and mother are alive and well; two other children are alive and well, three are dead: one at the age of 7 years, one at 8 months, one at 3 days. There had been no stillbirths.

*Physical Examination.*—This reveals an undersized, anemic child with a hydrocephalic head. The thorax is normal in shape, and the thoracic organs are unchanged. The liver extends over two fingers' breadths below the costal arch on the right side. The liver edge is somewhat irregular. The spleen is not palpable. No fluid can be demonstrated in the peritoneal cavity. There is a firm swelling in the right abdomen between the liver and the crest of the ilium.

*Operation.*—The boy was operated on under ether anesthesia, April 10. A median abdominal incision was made, and a tumor the size of a child's head was found occupying practically the entire right abdominal cavity below the liver. The diagnosis of inoperable sarcoma of the right kidney was made, a drain was inserted, and the wound closed. Death occurred April 18, 1914.

*Necropsy*, eight hours after death (Dr. B. Roman).—The body is that of a male child, 88 cm. long, of slender physique and poorly developed musculature. The subcutaneous fat is sparse. The skin is brownish gray. Post-mortem rigidity is absent. The hair is thin and of a dark blond color. The pupils are narrow, the left slightly wider than the right. The teeth are in good condition. The neck is narrow. The lower part of the thorax is widened on account of the distention of the abdomen. The abdomen protrudes, especially in the right hypogastrium. In the midline above the navel there is an operation wound 10 cm. long, through the lower end of which a gauze drain protrudes. Only the right testicle is in the scrotum. The lower extremities are slightly edematous.

The skull is 51 cm. in circumference, and measures 17.5 by 11.3 by 0.2 cm. The sinuses of the dura contain liquid blood. The parietal bones on both sides are prominent. Their inner surfaces are smooth. The dura mater is adherent to the bones at the vertex of the brain. The leptomeninges are granular and rather moist. The brain weighs 1,370 gm. Its substance is pale and somewhat moist. The ventricles are slightly enlarged. The ependyma is smooth. The hypophysis is slightly enlarged. The surface made by section is of normal color and configuration.

The thyroid gland is somewhat enlarged, yellowish in color, and of normal consistency.

The submaxillary lymph-nodes are enlarged to the size of hazelnuts. Their cut surfaces show reddish and grayish mottlings. The cervical lymph-nodes on both sides are of pea size, of reddish-gray color, and rather soft. The lymph-nodes in the left angulus venosus are enlarged to the size of beans. One of these contains a necrotic area 5 mm. in diameter. The others are similar to the cervical nodes. Those on the right side are unchanged. The peritracheal lymph-nodes are enlarged to the size of cherries. They are grayish red and succulent. The upper right tracheobronchial glands are enlarged, and one of them has a yellowish nodule at its upper pole. The left upper tracheobronchial nodes are like the paratracheal on this side. The lower tracheobronchial nodes

have grown together to form a packet about the size of a small walnut. On the surface made by section these are seen to be composed of grayish-red nodules. The largest of these is 0.7 cm. in diameter. The bronchopulmonary lymph-nodes on the right side are about the size of hemp seeds. They are gray and succulent. The interlobar-pulmonary lymph-nodes on the right side are of pea size. Several of them have grayish nodules near their periphery. Their fellows on the left side are similar in size, but free from nodules. The retro-mediastinal lymph-nodes form a packet about the size of a date. Cross-section reveals necrotic yellowish-gray nodules, the largest being about the size of a pea.

The thymus is bilobar; each lobe measures 2 by 1.6 cm., and extends from the lower pole of the thyroid gland to the base of the heart.

The pericardial cavity contains a small amount of a clear serous fluid. The pericardium is smooth. The heart is slightly enlarged. The myocardium is fairly firm and of a grayish-brown color. The left ventricle is somewhat dilated. The valves are unchanged. The foramen ovale is patent. The intima of the aorta is smooth.

The right pleural cavity contains a small amount of serofibrinous fluid. The right lung is free. The pleura on the base of this lung is covered with fibrinous exudate and contains a number of ecchymotic spots. The lung is rather bulky, and in the lower lobe its tissue is partly collapsed. The lung crepitates throughout. The upper lobe of the left lung is similar to that of the right, but the lower lobe does not crepitate and contains numerous pneumonic foci. The pleura of this lung is smooth. A purulent fluid can be expressed from the smaller bronchi of this lung.

The mucous membrane of the mouth is pale. The tonsils are the size of beans, and have enlarged lacunae. From one of these on the left side, pus is expressed.

The mucous membrane of the pharynx and of the esophagus is pale.

The peritoneal cavity contains about 100 c.c. of a purulent hemorrhagic fluid. The parietal and visceral peritoneum is covered with a purulent exudate. That part of it which covers the region around the hepatic flexure and the right kidney is very hemorrhagic. The loops of the small intestines are adherent to each other by a fibrinous exudate.

From the region of the right kidney a rather firm tumor protrudes. This has pushed the hepatic flexure forward and upward, and the adherent loops of intestine upward and to the left. The mass extends about five fingers' breadths under the costal arch. It is bounded above by the liver and the pyloric part of the stomach, below by the right anterior-superior spine of the ilium, and to the left by the spinal column. The tumor is a soft, grayish-brown spherical mass, measuring 9 cm. in diameter. It is surrounded by a rather thick connective tissue capsule, which is united to the upper pole of the right kidney. This mass with the adherent kidney occupies most of the space of the right half of the abdominal cavity. The cut section of the tumor is mottled, consisting of grayish-yellow, grayish-red, and dark red areas. The right kidney is markedly compressed from above, downward and inward, by the tumor. The right suprarenal cannot be found; it is apparently included in the mass.

The spleen measures 8 by 7 cm. At its upper pole it is covered by a fibrinous exudate. The surface made by section is grayish red. The follicles are not visible.

The stomach contains a moderate amount of a grayish semiliquid. The mucosa of the stomach is pale and partially softened. The duodenum and bile passages are unchanged.

The pancreas is somewhat compressed by the tumor mass. At the end of the pancreatic tail, there is an accessory spleen of about the size of a cherry.

The abdominal aorta is markedly compressed by the greatly enlarged periaortic lymph-nodes. They also compress the lumen of the vena cava to about

half its normal size. The nodes are closely connected to the tumor by connective fibers and are diffusely infiltrated by the tumor tissue. Similar glands surround and compress the left renal vessels. The lymph-nodes around the head of the pancreas are enlarged to the size of beans, and are grayish and succulent. So, also, are the paragastric lymph-nodes, and the nodes in the hilum of the liver.

The liver extends a hand's breadth below the costal arch. The right lobe of the liver is flattened out and compressed by the new growth. The tumor adheres to it. The capsule of the liver is partially covered with a fibrinous exudate. Numerous tumor masses of various sizes are seen in the liver parenchyma. Some of the external nodules have depressed centers. The remaining liver tissue is pale gray. The lobular markings are fairly distinct.

The left suprarenal is slightly enlarged and flat, and the medullary substance is markedly diminished in amount.

The left kidney measures 7 by 4.5 cm. Its capsule strips easily. Its surface is smooth. The pelvis and the ureter of this kidney are unchanged.

The mucous membrane of the urinary bladder contains numerous pin-point sized hemorrhages near the fundus. The urethra is unchanged. The testicles are small. The rectum is practically empty. The external genitalia are unchanged.

The mesenteric lymph-nodes are moderately enlarged, the largest being bean-sized. These are grayish-red to red in color.

The rest of the alimentary tract is unchanged.

In the body of the fourth thoracic vertebra there is an indefinitely outlined grayish nodule about the size of a pea. A similar, but smaller, nodule surrounded by a hemorrhagic zone occurs in the fifth thoracic vertebra.

The medullary substance of the left femur is dark red with yellowish-red mottlings. In the region of the proximal epiphysis occurs a hemorrhagic area, about 1 cm. in diameter, which at this place fills the entire medullary cavity. The medullary substance of the right femur is similar to that of its fellow, except that the former is more mottled. In the medullary substance of the right tibia, there occurs a grayish nodule the size of a hemp seed. There is a similar nodule in the medullary substance of the right ulna. The medullary substance of the left tibia, right fibula and left ulna are slightly mottled. That of the left fibula is unchanged.

In one of the left ribs there occurs a soft grayish-yellow nodule about 1.5 cm. in length. This entirely fills the medullary cavity of the bone.

*Bacteriologic Examination.*—From the peritoneal exudate, *Staphylococcus albus* was obtained in pure culture.

*Anatomical Diagnosis.*—Fresh laparotomy wound with partial healing. General, acute, seropurulent peritonitis. Serofibrinous pleurisy, right. Malignant tumor of right suprarenal (?) with compression and displacement of kidney and displacement of hepatic flexure. Metastases in the retroperitoneal lymph-nodes with compression and partial stenosis of the vena cava; in the retro-mediastinal; the right bronchopulmonary, the right lower tracheobronchial, and the left supraclavicular lymph-nodes; in the liver, the thoracic vertebra, and in numerous long bones. Slight hydrothorax with anasarca. Lobular pneumonia of the lower lobe of the left lung. Parenchymatous degeneration of liver, kidneys and of the heart muscle, with slight dilatation of the left ventricle. Catarrhal bronchitis. Old lacunar angina. Slight hydrocephalus. Patent foramen ovale.

*Microscopic Examination.*—Technic: The specimens were hardened in formaldehyd and Zenker's fluid, and embedded in paraffin and celloidin. Frozen sections were cut for Bielschowski's stain. The stains employed were: hemalum and eosin; iron hematoxylin; Van Gieson's stain; Mallory's connective tissue and neuroglia stains; Wiegert's neuroglia stain and also Alzheimer's stain for ameboid neuroglia stain; and finally Bielschowski's stain for nerve fibers.

The largest tumor is surrounded by a rather thick connective-tissue capsule from which trabeculae extend inward to form the framework of the new growth. On the inner surface of the capsule, there occur numerous remnants of the suprarenal cortex. In places these cells extend in narrow columns between the connective tissue fibers of the capsule; in other parts they form distinct nodules, which, in turn, are invaded by the tumor tissue. Most of the cortical cells are atrophic and degenerated. The posterior part of the capsule is free from these cells.



Fig. 1.—Photograph of main tumor and the neighboring organs. The tumor has been cut into halves and the surface made by section shows large areas of necrosis and numerous hemorrhages. The right kidney is compressed by the new growth. The liver is seen studded with tumor nodules.

The great bulk of the new growth itself is composed of cells averaging 8.5 microns in diameter. The individual cells are arranged either concentrically around fibrillar centers, or occur diffusely scattered. The concentrically arranged cells, termed by Küster<sup>8</sup> rosettes, form a conspicuous part of the tumor. The rosettes are round to oval, measuring from 26 to 54 microns in one diameter, and from 51 to 79 microns in the other diameter. Their periphery is formed of from twenty to thirty individual cells, which are usually arranged in a single layer. At times a more or less complete double layer is observed.

8. Küster, H.: Ueber Gliome der Nebennieren, *Virchows Arch. f. path. Anat.*, 1905, clxxx, 117.

The nuclei of these cells are slightly oval or round, and measure, in most cases, from 5 to 9 microns. They are rich in chromatin and have a distinct nuclear membrane. The smaller the nucleus, the richer it appears to be in chromatin; thus, the few nuclei present which are less than 5 microns stain very heavily, and the largest have a vesicular appearance. Mitotic figures rarely occur among the cells in the rosettes. The cytoplasm surrounds the nucleus as a delicate, thin zone, massed at the centrally directed end of the cell so as to form a sort of short stalk from which one or more fibrillae run to lose themselves in the central fibrillar structure of the rosette. The entire central structure is thus formed by these fibrils. Smaller cytoplasmic projections extend in other directions from each cell. In certain fields the fibrillar structure is especially marked, each cell sending out from one to eight fibrillae, which form a network. Nowhere in any section is there any tendency of the fibrillae to form parallel bundles. In certain portions of the tumors where rosettes are practically absent, the cells are closely packed and few fibrillae are seen. The nuclei of these cells are all more or less oval, and mitotic figures are more frequent than among the cells forming rosettes.

Throughout the tumor, large, oval nuclei, poor in chromatin, occur singly or piled one against the other forming clumps. These clumps consist of from three to ten nuclei, measuring 9 to 12 microns in diameter, and, where the tumor cells are diffuse, they are apparently without any cytoplasm. In most instances, however, these nuclei are connected with an undivided smaller or larger portion of cytoplasm, in which the nuclei sometimes lie near one end, thus simulating giant cells (Fig. 3). Structures of this kind are most numerous where the connective tissue is well developed, or just underneath the capsule where this contains remnants of the suprarenal cortex. Here these multinucleated structures form a large part of the tumor. In some places, the nuclei form a round ring about a center of undivided protoplasm. In other parts, groups of these large nuclei occur at the two poles of cytoplasmic masses. In still other places, one finds large areas of multinucleated cytoplasm, part of which is fibrillar, part homogeneous; and, also, an occasional small heavily stained nucleus definitely connected to the syncytium by fibrillae running directly into the undivided cytoplasm. There also occur two other structures among or near connective-tissue trabeculae and near the capsule of the tumor. One of these is a distinct type of large, often multinucleated cell in which the cytoplasm is abundant, and either round, unipolar, or multipolar. The nuclei are also rather large and have a distinct nuclear membrane and a large nucleolus. These cells are not numerous, are scattered, and show, in every case, distinct evidences of degeneration. Wherever these cells occur there are also found oval or round, hyaline bodies, measuring from 15 to 20 microns in diameter, lying among the connective tissue. These do not take the stain of corpora amylacea. The smaller tumor cells do occur in scattered heaps among these structures, but the syncytial tissue, the large polar cells, as well as the hyaline bodies, are absent in actively growing portions of the tumor.

The fibrillae in the center of the rosettes stain red with eosin, yellow with Van Gieson, but do not stain at all with Mallory's connective tissue stain. With Mallory's neuroglia stain most of the fibrillae take a light blue color; but a few wiry fibrillae, both within the rosettes and outside, stain a heavy blue. Wiegert's neuroglia stain gives a negative result. Alzheimer's stain for ameboid glia cells stains cytoplasm and fibrillae, as well as almost everything else, blue. With Bielschowski's stain the center of the rosettes takes a brownish tinge, but repeated attempts failed to demonstrate any fibrillae which stain black. On the other hand a few distinctly black, rather thick fibers occurred near the large ganglion cells.

The connective tissue is scant in certain places throughout the tumor; in other places it forms over half of the substance. Between these two extremes variations occur. Where the trabeculae are thick, hyaline degeneration is



marked. Throughout the capsule, groups of tumor cells are abundant. They are seen forcing their way, as it were, between the bundles of supporting tissue. The vessels of the capsule are in many places crowded with cells from the new growth.

The blood-vessels enter the tumor through the trabeculae. They are abundant in places; in other portions they are not frequent; in all parts they are thin-walled and have wide lumina. Arteries cannot be recognized. The blood contains an unusually large proportion of polynuclear leukocytes. Smaller and larger hemorrhages are noted throughout, but in greatest abundance in what appears to be the older parts of the tumor. Some of them are recent; others seem old; a few are calcified. Frequently, the hemorrhages are associated with the areas of necrosis of the tumor cells. Such areas are also rather numerous so that some sections are composed almost entirely of necrotic cells. Then

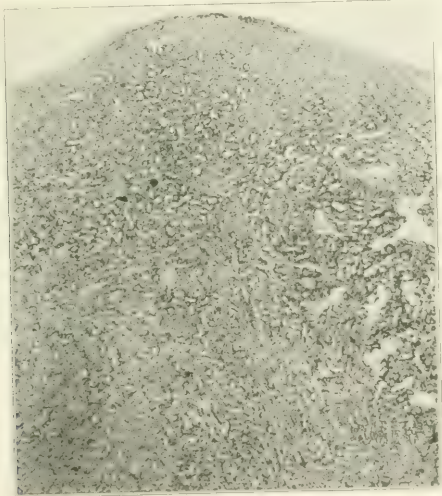


Fig. 2—Photomicrograph (retouched,  $\times 25$ ) of area from main tumor. The rosettes are very abundant, and the blood-vessels have wide lumina.

again, they are practically absent in others. All stages, from degenerated, poorly staining cells to complete coagulation necrosis and even calcification, occur.

The microscopic structure of the large nodules and of two of the smaller ones lying next to the main tumor is very similar to that described. The connective tissue is rather abundant, and among the connective tissue fibers are seen degenerated ganglion cells, and also single or grouped polygonal cells with large nuclei—evidently chromaffin cells. Rosettes are in some parts abundant. In the smallest of the three nodules, the cells are in general diffusely arranged, and mitotic figures are abundant. In certain fields of the large nodules, the fibrillae are numerous. Hemorrhages are frequent in all three. Large portions of the nodules are necrotic. Tumor cells occur in the lumina of many of the blood-vessels.

The remaining nodules in the abdomen are infiltrated lymph-nodes. Ganglion and chromaffinic cells are absent, the nodules being composed entirely of well-preserved or necrotic tumor cells. In these nodules, many lymph-vessels are filled with tumor cells.

The right lobe of the liver is markedly infiltrated with cells from the new growth. In the extreme right edge of the liver, necrosis is prominent among the tumor cells, but nearer the left lobe nodules of various sizes occur, which afford an interesting picture (Fig. 4). In these smaller nodules, the liver cells in places have been totally destroyed, so that only an occasional bile-duct is seen. Toward the periphery occur atrophic columns of liver cells, forming a sort of scaffold for the proliferating tumor cells. Rosettes are abundant and similar in size and structure to those already described except that a larger number of them have a double row of cells. Mitotic figures are rather frequent even among the nuclei of the rosette cells, and are very abundant in the cells outside the rosettes. The nuclei are somewhat irregular in size. The small, heavily stained ones are numerous, and many large (10 microns), round vesicular nuclei also occur. Here, as in the rest of the metastases, clumps of large, oval nuclei are scattered among the rosettes. Gland-like arrangements occur in some places. At the periphery of the nodules the tumor cells extend through the liver sinusoids. These are crowded with cells, and cell division is frequent. Thrombi consisting of tumor cells also occur in the portal veins. Along the periphery of the liver, just under and in the capsule, there is a practically continuous zone of tumor cells. About half of these are of the smallest variety described. The rest of the liver cells show a marked degree of parenchymatous degeneration.

The enlarged glands in the mediastinum and those around the trachea and bronchi all show metastatic nodules, but most of them are very necrotic. In these glands, rosettes and fibrillae are comparatively few.

Practically all of the long bones of the body show tumor metastases in the medullary substance. The structure is characteristic; hemorrhages occur, the fibrillae are exceedingly well developed, and the rosettes are abundant (Fig. 5). Here as in the other metastases, ganglion and chromaffinic cells are absent.

The lungs are free from metastases. The rest of the organs show no interesting changes.

#### COMMENT

The striking features of this new growth then are several. In the first place, it has all the earmarks of a malignant growth; for, on the one hand, its growth is infiltrative, as shown by the invasion of the suprarenal cortex by the tumor cells, by the cells breaking through the capsule and then forming nodules outside of it, and by the infiltration of the connective tissue of the liver. This infiltrative nature is distinct, but not so pronounced as in certain other tumors. Thus, it seems to have a certain respect for the organs, since nowhere have the tumor cells invaded the compressed kidney or any of the large blood-vessels whose lumina it had narrowed by its expansive growth. This respect for organs on the part of the tumor cells has been observed in other cases of this type. Both Landau and Herxheimer have called attention to it. On the other hand, true metastases occur. Pick and Bielschowski<sup>9</sup> have suggested a multiple origin for new growths of this

9. Pick, L., and Bielschowski: *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1911, vi, No. 4.

type. There can be no question but that the growths in the lymph-nodes and other organs, in this case, are secondary. Since the tumor cells are observed in numerous places both in the blood- and the lymph-vessels, it is evident that the elements of the new growth were distributed by means of both these channels. The tumor cells must first have reached the neighboring lymph-nodes, since the nodules here are the largest and show the most extensive necrotic areas. From these nodes the cells reached the main lymph trunks of the abdomen and extended upward, producing metastases in the nodules in the hepatic hilum, and from there entered the liver. It is also evident that the

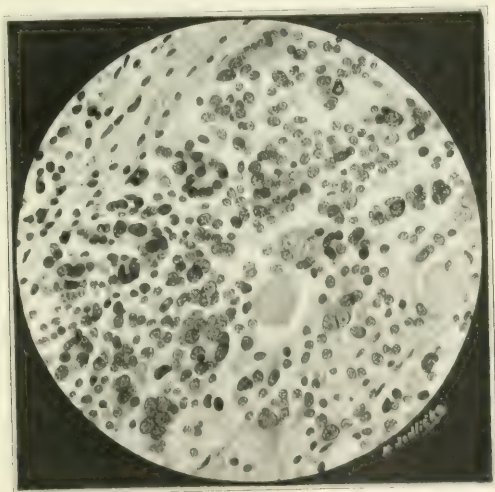


Fig. 3.—Photomicrograph (retouched,  $\times 370$ ) of area near capsule of the main tumor, showing multinucleated masses of cytoplasm and degenerated ganglia cells.

liver received implantations through the blood-stream. Following the lymph-stream further we see that the malignant cells involved the glands in the mediastinum, those around the bronchi and those in the neck. The cells, then, reached the venous circulation, first through invading the vessels of the new growth; second, by the thoracic duct, and thirdly, through the hepatic veins; thus, eventually, tumor cells must have reached the lung in numbers. A careful search of both lungs failed to reveal any nodules, yet the cells must have passed through the lung capillaries to reach the arterial blood in order to produce metas-

tases in the bones, for the multiple metastases in the various bones can be explained in no other way. Just why the bones alone should be involved cannot be accounted for. To-day, we only know that certain malignant tumors, such as neuroglioma of the retina, carcinoma of the prostate and of the thyroid, have a certain affinity for bone. The future must explain why. The most marked metastases occur in the liver. This is the organ most frequently involved in these cases; indeed, in some of the cases reported, the liver is practically the only organ containing metastases. Herxheimer believes that the reason lies in the fact that the liver forms a good medium for the new growth. It is also reasonable to suppose that it receives the greatest number of implantations. The bone metastases are interesting, in the first place, because of the general involvement of the long bones, and, in the second place, because of the beautiful rosette formation and fibrillae in these metastases. Bone metastases have been observed in less than one-half the cases reported. The statement is made by Landau and others that the growth in bone cannot be recognized as sympathicus tumor. In our case, this is certainly not true, as the growth could not be mistaken for anything else. Because of the fact that the tumor tissue is difficult to recognize macroscopically, and, also, because the bone-marrow is rarely examined as a routine, I am inclined to believe that metastases may be more frequent than reports would indicate.

In the second place, this type of new growth apparently occurs only in young children, and most of the reported cases have been in very young children. Indeed, if we except certain dubious tumors, such as the second case of Küster, and two of Wright's cases, the oldest case reported is in a child of 7. Among the twenty-eight cases, reports of which were collected by Herxheimer, twenty were less than 1 year, and twelve had not reached the age of 3 months; so that the case here reported must be considered as occurring in an unusually old child. The early occurrence of these tumors is of course very strong evidence for their congenital origin.

The third peculiarity of this tumor is its location. There can be no reasonable doubt as to the origin of the tumor in this case. Its location and the fact that in the capsule, as well as in the substance of the tumor, practically the entire cortex of the right adrenal was found, and also that throughout the tumor nervous remnants of the medulla occurred, show it to have sprung from the medullary substance of the suprarenal. Most of the tumors of this type have had their origins in the medulla of one of the suprarenals or have sprung from the sympathetic system near the kidneys. And every one has originated in some part of the sympathetic system. The fact that tumors so fre-

quently occur in the suprarenals must be borne in mind by the clinician in the differential diagnosis in this part of the body in the young.

Finally, this tumor has a structure which distinguishes it rather sharply from the other known types of malignant tumors. The rosette that forms such a conspicuous part of the cellular structure of this tumor is probably not identical with any other structure known. These are present in greater or smaller number in practically all tumors of this kind, and the fibrillar substance between the diffusely arranged cells is always present in greater or smaller amount.

The other features of this case, such as the frequent hemorrhages, the large areas of necrosis and the wide blood-vessels with exceedingly

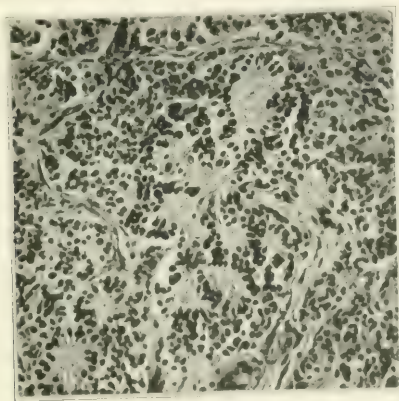


Fig. 4.—Photomicrograph (retouched,  $\times 75$ ) from small nodule in liver. The fibrillae of the rosettes stand out prominently.

frail walls, have been observed in all the other tumors of this type. The microchemical peculiarities, which make the fibrillae stain yellow with Van Gieson and make them fail entirely to react with the connective tissue stain, are also noteworthy. Therefore, the location of the tumor, its structure and the staining reaction of the fibrillae make it certain that the tumor cannot be classed either among the sarcomas or the ordinary carcinomas. Nor does it belong to the new growth of lymphatic tissues, the lymphosarcoma, which it simulates macroscopically, but must arise from neurodermal cells.

All present-day writers agree that these tumors are nervous in origin, but as to the particular nervous element from which they spring, there exist two opinions. One group believes that these tumors



are composed of so-called building cells of the sympathetic system and that the fibrillation observed is an attempt toward differentiation into nerve fibers. In other words, the tumors are what Herxheimer calls neuroblastomas. The other group holds the tumors to be malignant gliomas. Both these views are based, of course, on the resemblance which the various observers see between the elements of these new growths and the normal cells. In order to make the relation of these growths to the nervous elements more clear, a brief statement of the normal development of the sympathetic and the chromaffinic system is offered.

Kohn, Wiesel, Held<sup>10</sup> and others have shown that certain cells from the neural canal become the mother cells of both the sympathetic and the chromaffinic systems. Wiesel holds that some of these building cells wander into the suprarenals to form the medulla, and that these cells (for the most part) give rise to chromaffinic cells, but that from them also spring the ganglion cells and other nervous elements of this organ. But Zuckerkandl<sup>11</sup> holds that the cells which wander into the adrenal cortex later develop only into chromaffinic cells, or, at least only in exceptional cases, give rise to other nervous elements. Held has further shown that, as a first step in differentiation, the sympathetic neurocyte undergoes a fibrillation of its cytoplasm. Finally, Held has shown that glia cells also occur in the sympathetic system, and that this glia tissue differentiates from heaps of large oval nuclei lying in undifferentiated cytoplasm—a true syncytium. It is also to be borne in mind that Kohn has shown that young chromaffinic cells occur in two forms, as a syncytium and as heaps of cells, and that in man the syncytial form predominates, but that the clumps also are found.

Based on this somewhat conflicting knowledge of the embryonal development of the sympathetic system, Wright, Landau, Herxheimer and Martius<sup>12</sup> hold that this type of tumor comes from sympathetic formative cells, and that its cells have a tendency to develop into true nerve cells. The reasons they give for their position are positive as well as negative. In the first place, Wright sees a striking similarity between groups of tumor cells and those of the sympathetic nerve cells in young children. He also finds bundles of fibrillae running parallel to each other in the tumor in very much the same way that the nerve

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10. Held, H.: *Die Entwicklung des Nervengewebes bei den Wirbeltieren*, Leipzig, p. 378.

11. Zuckerkandl, E.: *Keibel-Mall, Handbuch der Entwicklungsgeschichte des Menschen*, Leipzig, 1910, xi, 157.

12. Martius, K.: *Maligner Sympathoblastoma des Hals-sympathikus*, *Frankf. Ztschr. f. Pathol.*, 1913, xii, 442.



fibers do in the young ganglia. Then, he fails to stain the fibrillae with Mallory's neuroglia stain.

Landau has also observed the parallel arrangement of the fibrillae. He further adds that the cells of the new growth are capable of differentiating into higher nervous elements, so that the older the individual, the more differentiated the cells. Thus, ganglion and glia, as well as chromaffinic cells, may appear in this type of tumor when older children are affected. Martius supports Landau's theory by a case of a tumor from the cervical sympathetic in a 2½-year-old child, in whom well-developed ganglion cells occurred. At first glance, it may seem as though our tumor also lends proof to Landau's contention. But the nervous and the chromaffinic elements found in this

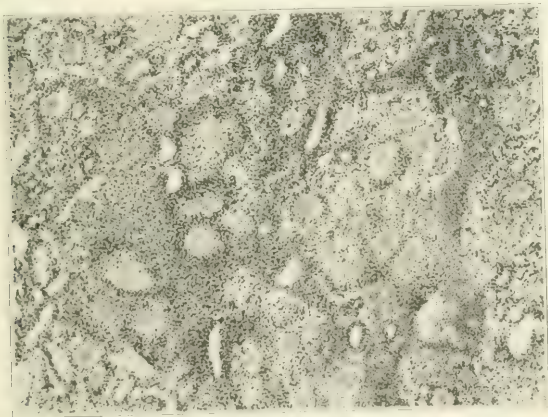


Fig. 5.—Photomicrograph (retouched,  $\times 50$ ) from metastasis in one of the long bones.

case probably do not belong to the blastoma, since they occur only where such tissue normally are found, and in normal amount without sign of proliferation, but rather of marked degeneration. Landau admits the possibility that these tumors may contain neuroglia cells, but does not believe in their gliomatous nature, because the fibrillae do not take the glia stains, because glia cells are higher differentiation products and because the rosettes are widely different from the glia rosettes.

Herxheimer supports the arguments advanced by Wright and Landau. He applied the Bielschowski stain and found that the fibrillae stained black. This he considers conclusive proof that the tumor is a neurocytoma.

The evidence cited is not invulnerable. Thus Wiesel's conclusion that the formative cells of the sympathicus enter the suprarenals is not accepted by all. The similarity between the tumor cells and the young sympathetic ganglia, emphasized by Wright, does not appear striking to me. And it is curious to note that the arrangement of the fibrillae into parallel bundles, noted by Wright and made much of by Landau and Herxheimer, occurred most strikingly in the case of Wright which both Landau and Herxheimer agree does not belong to this type of new growth. It may also be questioned whether the similarity between the fibrillation occurring in sympathetic neurocytes as seen by Held, and the fibrillae of these new growths, should warrant the emphasis laid on it by some. Herxheimer admits that both connective-tissue fibers and nerve fibers stain with Bielschowski. It must also be borne in mind that the section stained is from the medulla of the suprarenal where nerve fibers normally are abundant. He failed to find any nerve fibers in the other metastases. In the case here reported, repeated attempts with Bielschowski stain failed to stain any of the fibrillae black.

Those who consider these tumors malignant gliomas include Virchow,<sup>13</sup> Küster, Lapointe and Lacene<sup>14</sup> and Schilder. They are less certain in their assertions. Thus, Virchow speaks of the tumors as glia-like, and Küster states that, since they are more like gliomas than any other tumor, he ventures the name "malignant glioma." The main points on which this view is based are, first, that the tumor cells are strikingly like neuroglia cells, and second, that the interlacing fibrillar network in this type of tumor cannot be distinguished from such network found in gliomas. Neither of these points can be gainsaid. These authors also assert that rosettes occur in gliomas. It is true that most of the glia rosettes are not identical with the structures here known as glia balls, spheres or rosettes. Landau's statement that these could not possibly be mistaken for glia rosettes is too strong, for there does occur in the tumors, known as neurogliomas of the retina, rosettes very similar to these.

Schilder rightly calls attention to the fact that unripe glia fibrillae do not take the specific stain for neuroglia; thus, tumors undisputably neurogliomas often fail to take the glia stains. Besides, Weigert's stain is notoriously uncertain even for normal glia fibrillae. In this case, some of the fibrillae in most of the rosettes stained deeply with Mallory's neuroglia stain.

In conclusion, I wish to call attention to the many similarities between this type of new growth and the neuro-epitheliomas or neuro-

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13. Virchow, R.: *Die krankhaften Geschwülste*, 1864, ii, 150.

14. Lacene, cited by Landau (Footnote 6).

gliomas of the retina. Both types occur in the young; both are composed of cells with chromatin-rich nuclei and fibrillar cytoplasm; both have rosettes; both are malignant with tendency toward multiple bone metastases.

It does not seem to me that we have at the present time evidence enough to place this new growth either among the neurocytomas or the neurogliomas. The matter of classification is of minor importance. Certain it is that we are here dealing with a malignant sympatheticus tumor.

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## UREMIA

### III. THE NON-PROTEIN NITROGEN OF BLOOD \*

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The nitrogen-containing crystalloids of blood have interested physiologists and clinicians for almost a century and in some respects the questions at issue are but little clearer to-day than in the time of Bright. Methods of research have changed and the data secured are more accurate, but it is remarkable in reviewing the literature that many of the conclusions of the later investigations are a simple rewording of the earlier. The facts have, however, been amplified and our knowledge made more complete without as yet any unanimity of opinion as to the significance of these facts. The amount of data at our disposal now is not inconsiderable and it may not be a useless task in the beginning to survey this field.

Urea was first detected in the urine (*matière savonneuse*), by Rouelle, Jr., in 1773, and in 1821 Prevost and Dumas observed an accumulation of urea in the blood of dogs following extirpation of the kidneys. It was this latter observation particularly which led Bright's assistants Prout, Babbington and Christison,<sup>1</sup> to analyze the blood of nephritic patients. From the fact of finding urea in the blood of patients with severe nephritis the name of the syndrome, uremia, took origin. It was not learned till some time later that urea is only slightly toxic. Investigations bearing on the urea content of blood were taken up by German and French clinicians and quantitative determinations attempted. Babbington and Christison had made some estimations of the amount of urea in body fluids. Their method was to desiccate the blood or fluid and then reduce the dry residue to a fine powder which was repeatedly extracted with alcohol. From the alcohol extract, on addition of nitric acid, crystals of ureanitate separated out and were collected and weighed. By this method 15 grains of urea were recovered from 1,000 grains of blood. Urea was also found in the fluid of the ventricles of the brain. Picard,<sup>2</sup> also using alcohol as a specific urea solvent, investigated the relation that the amount of blood-urea bears to the taking of food. Estimating the urea by Liebig's titration

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1. Bright: *Guys Hosp. Rep.*, 1836, 1, 339.

2. Picard: *Thèse de Strassburg*, 1856.

method, he found from 0.05 to 0.07 per cent. during fasting and from 0.11 to 0.13 per cent. after food. The methods at the disposal of investigators at this period were not accurate and the results only approximate. The blood-proteins were either precipitated by alcohol or by means of a salt, such as sodium sulphate, and urea determined by the titration method of Liebig; or by measuring the carbon dioxide evolved on decomposition (Millon). Discrepancies and variations in normals are to some extent explicable on these grounds. Without entering further into specific details the net result of the earlier investigations indicated that the non-protein nitrogen (since the methods used determined more than urea) varies under normal conditions and is influenced by the ingestion of food; and that it is often above the normal maximum with grave cases of nephritis: 0.15 per cent. (Picard); 0.2 per cent. (Yvon); from 0.28 to 0.41 per cent. (Gréhant). Also that this supernormal increase occurs in some other diseases, notably cholera and typhus fever.

An elaborate reexamination of the whole field was conducted by Schöndorff<sup>3</sup> using methods in some respects more accurate than those of his predecessors. He held a faulty conception of the range of substances precipitated by phosphotungstic acid, which does not, however, seriously detract from the value of his work. The earlier work was confirmed by Schöndorff in so far as his clinical material permitted. From the clinical aspect the important observation was, that of the total non-protein nitrogen in blood, urea composes a variable fraction; in the blood of a dog 79.6 per cent. of the total nitrogen, and in that of a man with dyspnea 56 per cent.

During the period since Schöndorff a considerable amount of careful work has been conducted by methods which, although not always entirely accurate, yet are sufficiently good so that the results may be considered. The chief obstacle in determining non-protein nitrogen in the blood has been the primary separation of the proteins. To effect this end a number of procedures are now in current use and will be reviewed, since I have controlled them by intercomparison, using the Kjeldahl method for nitrogen. The common method of protein separation by coagulation with heat and acid can not be used since protein is somewhat hydrolyzed even on short exposure to heat in acid solutions. As a result the filtrate invariably contains some of the cleavage products—peptones, polypeptids, etc.—which vitiate the accuracy of the final results, even when sodium chlorid is added, as used by Ascoli. The amount of these substances formed is not large enough so that a normal blood might appear pathological; but the results by this method constantly run higher than controls by safer procedures.

3. Schöndorff: Arch. f. d. ges. Physiol. (Pflüger's), 1899, lxxiv. 307.

Coagulation by means of alcohol is one of the oldest methods and is still used. When one volume of blood is added to from eight to ten volumes of 95 per cent. alcohol the filtrate contains no protein. Alcohol is, however, an excellent solvent for lipoids; of these in the blood some, for example, lecithin, contain nitrogen. Determinations by this method also run slightly higher than they should and actually higher than the control determinations by colloidal methods. Either ethyl or methyl alcohol may be employed.

Hohlweg and Meyer devised a method wherein the diluted blood is made acid with dilute acetic acid and 5 per cent. solution of diacid-potassium phosphate and then half saturated with sodium chlorid. The method works well so far as biuret tests indicate freedom from protein.

Colloidal precipitating agents have come into extensive use in biological chemistry and the application of these methods has overcome one of the chief difficulties in the determination of sugar in blood.<sup>4</sup> For their use in nitrogen precipitations the chief inconvenience is that the blood or serum must be much diluted, which gives too large a filtrate volume for convenience in routine work. When, however, nitrogen partitions are being carried out with the filtrate, the volume is not an obstacle. It is possible that of some nitrogen-containing substances found in blood a small part may be adsorbed in the coagulum. There is no clear-cut evidence for this, however, as the values for total nitrogen check well with other methods. In practice two substances may be employed as precipitating agents, kaolin and dialyzed iron (*Ferrum oxidum dialyzatum*). Kaolin may be used with serum, but does not work well when hemoglobin is present; with whole blood it is necessary to resort to iron. The blood is diluted, one part to twenty of water; of a 10 per cent. solution of the iron there is added 2 to 3 c.c. for each c.c. of blood used, shaking constantly. The flask is allowed to stand half an hour then some electrolyte added—a gram of sodium sulphate. The volume is made up to mark, let stand an hour and then filtered.

For routine work a convenient method is the use of uranium acetate. The serum is diluted three times with water and an equal volume of 1.5 per cent. uranium acetate added. A water clear filtrate results, free of protein. In the dilutions employed uranium precipitates none of the crystalloids of blood.<sup>5</sup>

The method of determining the total nitrogen generally employed is the Kjeldahl. For urea Benedict's procedure, or Van Slyke's urease method, is most convenient, and gives dependable results. The various

4. Rona and Michaelis: *Biochem. Ztschr.*, 1908, vii, 329; viii, 121.

5. Aszacki: *Zentralbl. f. inn. Med.*, 1912, xlvii, 1166.



hypobromite methods still used by some French clinicians are wholly untrustworthy.

The non-protein nitrogen, or as it has been variously called, "filtrate" nitrogen, "rest" nitrogen, is a sum of several fractions, not all of which have been identified. As some of these substances may be increased in specific diseases without materially affecting the total (since nitrogen is but one element in the substance), our theme may be considered from several points of view. For example, in relation to uric acid, an uricemia has been noted quite uniformly in gout, pneumonia, leukemia, and with some cases of nephritis; and with all of these there is not necessarily a significant rise of the total non-protein nitrogen above normal, although this may occur in some instances. Likewise considerable rise in the values for ammonia-nitrogen may occur without appreciably influencing the total. From this it is evident that investigations may not be confined to total nitrogen but must include a consideration of the integral factors composing the non-protein nitrogen of blood.

With normal men the total non-protein nitrogen appears never to rise much over 40 mg.; or to fall much below 20 mg. per one hundred c.c. of blood, and the largest part of this is urea-nitrogen which fluctuates enormously. The extremes in my determinations are 92 and 46 per cent. urea-nitrogen for men apparently normal; more commonly 60 to 70 per cent. In order to avoid the influence of ingested proteins it has been my practice to take the blood in the morning between 10 and 11 o'clock, the hospital breakfasts containing but little protein.

Appreciable increases in the non-protein nitrogen in the blood have been observed in a number of different diseases besides nephritis. The rise accompanying cholera can possibly be explained in part as a result of the oligemia which is conspicuous in both the Asiatic and nostras types, and with the former there is frequently a complicating nephritis demonstrable at autopsy. With pneumonia an increase in the non-protein nitrogen has been in my experience exceptional and associated only with marked evidence of circulatory disturbance. Herter observed an increased urea content in the blood of some patients with pneumonia and suggested that all such cases be comprised under the term "uremia." The conspicuous cardiac disturbance with those cases of pneumonia in which the filtrate nitrogen was found abnormal, seemed possibly to explain the accumulation on a circulatory basis and led me to an investigation of some cases of pure decompensation due to valvular disease. In selecting cases for this series only young individuals were utilized. Of the series here reported the ages ran between 18 and 26 years. It was attempted further to exclude

those cases in which an antedating disease such as scarlet fever would lend an etiological basis for a persistent renal change. The cases in this series all presented extreme degrees of decompensation when they were admitted to the hospital; cyanosis, dyspnea, edema, hydrothorax, congested and often pulsating livers, oliguria. An initial albuminuria usually subsided or vanished when the cardiac condition improved. It has usually been stated that broken compensation, unassociated with renal change, does not occasion an increase in the non-protein nitrogen of the blood, and with the lesser degrees of circulatory embarrassment the facts do not run counter to theory. But with the severest manifestations of this disorder it would be difficult to understand how those conditions which bring about in some cases almost or complete anuria should not also lead to a heaping up in the blood-stream of the materials excreted normally through the kidney. There is also with these cases an increased katabolism coincident with the fever which is almost invariably present.

TABLE 1.—NON-PROTEIN NITROGEN FINDINGS IN CIRCULATORY DISTURBANCES  
NOT NEPHRITIC

Diagnosis	Non-Protein N.
1. Cardiac, valvular .....	40
2. Cardiac, mitral stenosis .....	59 †
3. Cardiac, aortic insufficiency .....	61 †
4. Cardiac, aortic insufficiency .....	47
5. Cardiac, mitral stenosis; cerebral embolism....	53
6. Cardiac, mitral and tricuspid.....	{ 73 †
	{ 85
7. Cardiac, mitral and tricuspid.....	90 †
8. Cardiac, aortic .....	43

† Necropsy.

The cases reported in Table 1 suggest, at least, that an increase in the filtrate nitrogen can be a result of purely circulatory disturbances. In but four of these cases was the absence of a nephritis confirmed by necropsy. The kidneys in these instances presented the typical picture of cyanotic induration. The cell infiltration was relatively slight and the epithelial change just apparent. The average non-protein nitrogen in the cases reported is 61 mg. per hundred c.c. of blood with 40 mg. and 90 mg. as the extremes.

If these results can be confirmed by other students of these diseases the fact involved is important as indicating the part played by the circulation in a picture already recognized as composite. It also has relations to diagnosis.

The significance of the non-protein nitrogen in renal diseases may be considered from a number of aspects; concerning its bearing on diagnosis and prognosis much has already been written and too often not in a judicial tone. The relation to anatomical and physiological conditions has been less considered primarily due to the fact that

nephritis in man involves all the renal structures to some extent and the physiological questions are complicated by a subtle perversion of the whole metabolism.

The following cases are some of those observed during the last two years and are selected on the basis of completeness of the clinical data secured during the period of observation in hospital. In most instances a number of blood determinations have been made in each case and when these vary, one from another, to a significant degree they are recorded.

TABLE 2.—NON-PROTEIN NITROGEN IN NEPHRITIS WITH AND WITHOUT UREMIA

Case No.	PARENCHYMATOUS NEPHRITIS	WITHOUT UREMIA	Remarks
	Non-Protein N.	B. P.	
19	61	160-190	Post-pneumonic.
101	62	100-130	Edema, anemia.
	74		
	71		
	70		
104	61	140	Edema.
	43		
107	70	120-140	
WITH UREMIA			
5	39	.....	Oliguria, edema, convulsions.
131	115	.....	Convulsions; at autopsy, large white kidney.
Case No.	CHRONIC INTERSTITIAL NEPHRITIS	WITHOUT UREMIA	Remarks
	Non-Protein N.	B. P.	
1	38	150-70	Cardiac symptoms.
	42		
2	45	150-160	Lassitude, gout.
3	74	160-180	Edema.
	70		
6	64	180-220	Headache; died in two months.
7	14	200	Headache, edema; died in three weeks.
	22		
8	47	180	Dyspnea, nausea.
52	132	200-150	Dyspnea, edema; died after five months.
(one month later)	45		
57	48	170-220	Headache, dyspnea; died.
58	120	200	Edema.

Of the first group only exceptional cases are here recorded. These cases of parenchymatous nephritis indicate that the non-protein nitrogen in this type of renal lesion is not necessarily low; Case 101 was of particular interest. The patient was kept on a weighed and analyzed diet (7 to 8 gm. of nitrogen per day) for over a month. At the time of his first determination (62 mg.) he was in bed and there was massive edema. There was a rapid loss of water and a subsidence of the edema which was accompanied by a rise in the non-protein nitrogen notwithstanding a large negative nitrogen balance.

The special interest that resides in cases of this character is the relation the "rest" nitrogen holds to water accumulations in the body. It has been suggested in explaining the relatively slight rises of the non-protein nitrogen with parenchymatous nephritis that the water retention effects a dilution and hence masking of the true state of affairs.

Case 131 was thought on account of the high non-protein nitrogen to be one of chronic interstitial nephritis with an acute exacerbation to explain the urine picture. The necropsy revealed a typical large white kidney.

As a rule, my results with parenchymatous nephritis agree with those of other investigators. The lowest figure is 32 mg. and the highest 115 mg. (uremia, Case 131) with an average of 63 mg. When uremia occurs, I have the impression that the "rest" nitrogen is often 150 mg. or over, since a number of cases of uremia in which high values were found were apparently due to parenchymatous nephritis; but in the absence of pathological examination proof is wanting. Strauss found an average of from 62 to 63 mg. in four cases of this type of renal lesion, with uremia and 80 mg. as a maximum. With the transitional types of nephritis there is at once an increase of values up to 120 mg. as an average in cases with uremic symptoms. Estimations of this character conducted with cases of nephritis in which there is water retention would be most instructive if they were combined with estimations of the whole blood volume. The significant observation of Strauss that edema fluids contain practically the same amounts of non-protein nitrogen as the blood has been adequately confirmed, and this fact offers an inviting explanation for the appearance of uremic symptoms with some cases following on the rapid loss of water (diuresis or diaphoresis). Case 101 illustrates the increased concentration that at times may occur even when there is a hyperazoturia, as the metabolism study indicated in this instance.

When we turn to the various types of contracted kidney the non-protein nitrogen tends to assume somewhat higher values, with notable exceptions, however, even in the uremic states. The average values for my first series of seventy-two cases was 87 mg., including cases of uremia; and this average has been reduced slightly, 84 mg., in the total determinations made to date in 130 cases. With cases free of uremic manifestations Strauss' average was 82 mg., which jumped to 130 mg. when there were uremic complications. Maximal determinations are recorded over 300 mg. without uremia (Folin) and below 50 mg. with uremic symptoms (Ascoli, Farr and Austin, Foster). An especial interest is attached to low values in interpreting the usefulness of these determinations as a diagnostic measure; the import of a high non-

protein nitrogen has been sufficiently explained in the literature, often ignoring or failing to recognize as uremia cases in which low values obtain. That severe grades of chronic nephritis do occur without appreciable rises of the "rest" nitrogen and that such patients may even develop a fatal uremia the accompanying tables attest. That these cases may not be the rule is granted, but I do not think they are as exceptional as they are commonly held to be. With frank uremic manifestations we encounter many cases in which the non-protein

TABLE 3.—CHRONIC NEPHRITIS WITH UREMIA

Case	Nitrogen mg.	Blood-Pressure	Type	Termination
1	68	160 +	Asthenic	Improved
2	56	160 +	Asthenic	Died
5	110	160 +	Conv.	Died
7	62	150	Conv.	Died, 1 mo.
8	52	170	Asthenic	Died, 6 mo.
10	47	180	Asthenic	Died
14	72	220	Coma	Died
15	41	170	Asthenic	Died
16	198	250 +	Conv.	Died
18	178	200 +	Conv.	Died
22	65	160 +	Asthenic	Died
23	104	160	Asthenic	Died
24	86	200 +	Conv.	Died
26	40	280	Asthenic	Died
27	134	200	Conv.	Died
..	142			
28	44	160	Asthenic	Died
29	41	210	Asthenic	Died
..	70			
30	177	180	Asthenic	Died
31	21	200	Asthenic	Improved
32	136	210	Conv.	Died
33	100	160	Asthenic	Improved
..	116			
..	96			
34	239	190	Conv.	Died
36	61	100-80	Asthenic	Died
43	98	120-130	Stupor	Died
47	75	170-200	Conv.	Died
60	46	200-250	Stupor	Died, 1 wk.

nitrogen is not higher than is observed with cases of latent nephritis quite free of renal symptoms. This becomes at once evident if one examines the blood of patients in the surgical wards who regard themselves as in perfect health except for the fracture or hernia which brought them to the hospital.

It is difficult to attempt to correlate the blood findings with any particular manifestations of the disease because of the variability of the latter, and this is particularly true of the blood-pressure, which

changes considerably from hour to hour. I have selected a fairly representative figure for systolic pressure from the day on which the blood was taken, or have used the low level and marked with a plus sign (Table 4).

A rough average struck by means of the data in Table 4 supports the current view at least in so far as it shows that the more pronounced degrees of nitrogen retention are prone to be associated with increased arterial systolic pressure.

TABLE 4.—VARIATIONS IN SYSTOLIC PRESSURE IN CASE WITH AND WITHOUT UREMIA

WITHOUT UREMIA	
Blood-Pressure, Mm. Hg.	Non-Protein Nitrogen, Mg. Per Cent.
150-170	42
170-190	63
190-210	67
WITH UREMIA	
150-170	73
170-190	78
190-210	120
210-250	108

It is of some moment to consider the types of uremic manifestations in association with the non-protein nitrogen. The symptoms of uremia are so various in their combinations that all the notable factors cannot be brought into this relation. Disregarding subordinate considerations, uremia is sharply divided into two classes by the presence or absence of convulsive seizures. When convulsions are wanting, the notable element in the symptom-complex sooner or later is asthenia, physical and mental, which grades off into stupor and coma. In Table 3 there are nine cases of the epileptiform type of uremia and seventeen of the asthenic—about the relation they bear to each other in incidence. For the convulsive cases the non-protein nitrogen averages 135 mg.; the extremes being 62 mg. and 239 mg. For the asthenic types the average is 67 mg., with 21 mg. and 177 mg. as the low and high values. There appears, then, to be some relation which the non-protein nitrogen holds to the character of the uremic manifestation; the higher values are observed more commonly in epileptiform uremia.

Of the uremic patients whose cases are here reported only three lived longer than six months; hence it is evident that we can draw no conclusions from these data as to the prognostic significance of the "rest" nitrogen in uremic states. In the absence of uremic symptoms, the non-protein nitrogen has, when the values are high, a definite prognostic significance.<sup>6</sup> With over 100 mg. the outlook is extremely grave.

6. Foster, Nellis B.: Pathological Deviations in the Chemistry of Uremic Blood, *THE ARCHIVES INT. MED.*, November, 1912, p. 414.



But this fact applies only to a fraction of the cases examined and it cannot be overlooked that values which are but slightly above normal fail to exclude a not remote fatal issue. Table 3 supports this statement in regard to uremia.

Thus far the non-protein nitrogen has been considered as a whole. Its composition is of interest both clinically and pathologically. In a former paper<sup>6</sup> data were given indicating the fluctuation of the urea fraction of the total nitrogen as between 35 and 80 per cent., and also some determinations of the purins and nitrogenized lipoids. These investigations have been broadened to include all of those nitrogen-containing substances known to occur in urine, since it seemed highly desirable to have better knowledge concerning the catabolic products influenced by diminished renal function, and also at the same time, any other substances that make up the total nitrogen with those cases of uremia in which the urea-nitrogen forms but half or less of the total nitrogen.

For the estimation of ammonia in blood the customary aeration method has been employed. As the amounts of ammonia are small, it is necessary to use hundredth-normal acid and alkali. Excellent controls are secured with iodo-eosin in ether as an indicator. The amount of ammonia-nitrogen in normal blood seldom rises above 0.5 mg. per hundred c.c. by this method. Winterberg<sup>7</sup> found 0.6 mg. and 1.3 mg. as the limits of normal, depending on the influence of taking food. Folin's<sup>8</sup> results average 0.1 mg.

There is a decided increase in the ammonia of blood with many diseased states, the highest values having been noted with diabetic coma. Winterberg also observed 2 mg. or more with infectious diseases. With the bloods of uremic patients my results may best be summarized; 28 cases were examined. In 11 instances the ammonia-nitrogen was below 0.5 mg.; that is, normal. With 12 the values were between 0.7 and 1.6 mg.; and with 3 between 1.8 and 2.2 mg. per hundred c.c. of blood. The highest values were found with cases of the convulsive type of uremia when the total nitrogen was high. Winterberg found slightly over 2 mg. of ammonia nitrogen with two cases of uremia, while Folin's figures range from 0.6 to 1.0 mg. for uremic bloods. The net result of these estimations indicates that ammonia accumulates in the blood in something over half of the cases of nephritis with uremia, and that exceptionally this increase may be considerable; but it tends to bear a normal relation to the total non-protein nitrogen.

7. Winterberg: *Ztschr. f. klin. Med.*, xxxv.

8. Folin: *Jour. Biol. Chem.*, 1914, xvii, 488.

The earlier estimations of the uric acid in blood are of doubtful accuracy on account of the method employed, yet the opinion has been long held, and is borne out by the recent work of Folin and others, that with renal disease there is uric acid retention. For the purpose of my study it seemed more advisable to determine the total purin content of the blood by a double precipitation with the Kruger-Schmidt method. The purin-nitrogen of normal blood varies from 3 mg. to 6 mg. per hundred c.c. of blood. With nephritis the average is higher than normal, although the increase with the parenchymatous types is much less apt to occur and is of less pronounced degree than with contracted kidney. With uremic patients the purin-nitrogen may reach 16 mg. in exceptional instances; the average for ten cases was 12 mg. in my series. No relation whatever can be detected between the total non-protein nitrogen and the purin nitrogen. The highest values for the latter may accompany only moderate increases of the total nitrogen, and in one case with a high total, 311 mg., the purin nitrogen was but 7 mg. Folin's<sup>9</sup> estimations of uric acid in relation to the total nitrogen show the same absence of concordance.

Estimations of creatin and creatinin were made in but four instances, as sufficient blood was not available with other cases. The proteins were separated out by the adsorption method of Rona and the filtrate concentrated. After hydrolysis with acid the readings were made using Shaffer's modification of the Folin method. The four cases studied were all of the convulsive type. The estimations in these four cases were 28 mg., 27 mg., 32 mg. and 46 mg., respectively. There is then so far as this evidence goes a considerable retention of either creatin, creatinin, or both as result of the renal lesion.<sup>10</sup>

It remains to consider the amino-acids, four estimations of which were done by the Van Slyke method.<sup>11</sup> The four cases were selected so as to represent various degrees of accumulation of non-protein nitrogen from 188 mg. down to normal. The amino-acid content was normal in all, 4 to 6 mg.

The history of the theories of causation of uremia is an epitome of the supposed toxic action of the various fractions which compose the non-protein nitrogen of blood. Each of these substances is in a certain degree toxic but not in the concentrations found in body fluids. While it is conceivable that certain cells, as, for example, nerve cells, may under some circumstances, exhibit, as Strauss has recently suggested, an increased irritability to these agents, yet such an idea is purely conjectural. That none of the substances with which we are

9. Folin: *Jour. Biol. Chem.*, 1914, xvii, 489.

10. Myers and Fine: *Proc. Soc. Exper. Biol. and Med.*, 1914, xi, 132.

11. Due to the courtesy of Dr. Donald Van Slyke.

familiar is to be held accountable for uremia is attested by excessive accumulations of these substances in certain morbid states without characteristic symptoms. Herter analyzed forty-one cases of anuria (not nephritis) recorded in the literature; with seven the anuria persisted for fourteen days or longer; and with these no symptom which could be regarded as uremic appeared before the eleventh day. It is well known that cases of poisoning with bichlorid of mercury present very few symptoms other than those due directly to the poison; yet the blood in such cases has yielded some of the highest values for "rest" nitrogen recorded. Whatever may be the significance of the known fractions composing the non-protein nitrogen, clinically or pathologically, it seems highly improbable that they are directly related as a cause to uremic manifestations. With some cases of uremia the sum of these known fractions practically equals the total nitrogen; while with other cases there is an appreciable unknown, undetermined fraction. Studies on this point are now in progress.

Concerning the location of renal lesions which induce faulty nitrogen elimination we have no conclusive evidence. With clinical nephritis of even the least complex types there is enough involvement of all the renal structures to make conclusions as to function hazardous. Experimentally induced nephritis offers some interesting data which it is difficult in many instances to harmonize with the clinical facts. There is an increase in the non-protein nitrogen with nephritis caused by poisoning with uranium, chromium and tartaric acid. All of these produce<sup>12</sup> lesions which are almost wholly tubular, any glomerular implication being inconstant and of slight degree. Arsenic involves both glomeruli and tubules, the lesions of the latter are earlier and more transitory than in the glomerulus; and according to Karsner it is during the period when the tubules are suffering, up to seventy-two hours after administering the poison, that the non-protein nitrogen shows its largest values. The highest values were also noted in association with the greatest tubular damage. The nearest approach to a pure glomerular nephritis that can be experimentally induced is by means of diphtheria toxin, but there is here also cloudy swelling and focal necrosis in the tubules. There is with this form of nephritis also considerable increase in the non-protein nitrogen of the blood.

The trend of evidence points to tubular rather than glomerular involvement as the important factor in nitrogen retention, since the phenomenon is clearly manifested with experimental renal lesions that are almost, if not entirely, epithelial. It is then of considerable interest that the nearest approach to a purely tubular nephritis clinically is not

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12. Folin, Karsner and Denis: *Jour. Exper. Med.*, 1912, xvi, 789. Karsner and Denis: *Jour. Exper. Med.*, 1914, xix, 263.

marked by the highest degree of nitrogen retention. (The possible deception due to edema has been already noted.) There arises then the question of degrees of structural damage in relation to function. With the contracted kidney there is so much destruction of all renal elements that it becomes quite impossible to assert that one structure is more damaged than another.

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# THE EFFECT OF ANESTHESIA AND OPERATION ON THE KIDNEY FUNCTION, AS SHOWN BY THE PHENOLSULPHONEPHTHALEIN TEST\*

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The question of the effect of anesthetics on the kidney has long been one of interest, and it seemed to us that an investigation of this by means of the phenolsulphonephthalein test of Rowntree and Geraghty would be of considerable interest. No extensive investigation of the subject in this manner has come to our attention, though a brief report is given by Sanford<sup>1</sup> who did the test in a series of cases of ether and gas-oxygen anesthesia, doing it first twenty-four hours before operation and again within a few hours afterward. He says:

The cases of gas anesthesia gave almost the same output of phthalein after anesthesia as before, showing apparently no effect on the kidney from the anesthetic. The ether cases have been rather contradictory. In short anesthetics the output of the drug was almost doubled after ether, and in long operations it was generally diminished. It seems probable that a short ether anesthetic is a renal stimulant, while a longer one is a depressant. So many factors enter into a renal functional test done within a few hours after an operation, that this can only be a conjecture.

Also in a recent article Block<sup>2</sup> reports about twenty cases tested with phenolsulphonephthalein before and after operation, and says that although the series is too small to serve as a basis for definite conclusions, it seems to indicate, among other things, that the effect of anesthesia on healthy kidneys is practically nil so far as reducing the excretory power goes; the duration of anesthesia in any given case does not of itself signify the amount of injury which the kidneys will sustain; the excretion of phenolsulphonephthalein after, as compared with before operation, is not affected by the administration of proc-toclysis, the position of the patient on the table or the character of the operation; and that in about one-third of the cases there is increased excretion after operation.

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\* Submitted for publication June 22, 1914.

1. Sanford: A Clinical Study of the Elimination of Phenolsulphonephthalein by the Kidneys, with a Report of 150 Cases, *Cleveland Med. Jour.*, 1912, xi, 763.

2. Block, Frank Benton: The Effect of Operation on Kidney Excretion as Indicated by the Phenolsulphonephthalein Test, *Jour. Am. Med. Assn.*, April 25, 1914, p. 1309.

A great many articles have appeared on the effect of anesthetics on the kidney as shown by the presence of albumin, blood, pus and renal elements, and to these brief reference will be made. Bovée<sup>3</sup> found that during the first fifteen minutes of ether anesthesia there was an increase in the output of urine, followed by a decrease up to forty-five minutes, after which it increased again. The diminution in urea output was even greater in proportion than that of the urine. He says that ether, carefully and skilfully given, has little effect on the production of albumin and casts, inducing them in some cases and stopping them in others. He states that in the Trendelenburg position there is even greater interference with urinary excretion, due, he thinks, partly to retraction in the renal pelvis and partly to a certain degree of arrest of renal function directly due to the position. Hewitt<sup>4</sup> has collected interesting figures from various authors as follows:

Weir.....	34 ethers, followed by 9 cases of albuminuria
Barenfeld.....	150 ethers, followed by 2 cases of albuminuria
Butler.....	500 ethers, followed by 1 case of albuminuria
Kute.....	600 ethers, followed by 1 case of albuminuria

Hewitt, summing up the question, says:

With regard to the frequency of renal complications after ether it is difficult to speak with certainty, owing to the fact that statements made by those observers who have specially studied this point are very conflicting. The author has not, to his knowledge, met with any cases in which such complications have occurred, but it is only fair to say that anesthetists' opportunities for ascertaining the condition of patients after anesthesia are very limited.

Buxton and Levy (quoted by Hewitt<sup>4</sup>) are "unable to satisfy themselves that ether, when properly administered, exerts any unfavorable influence on the kidneys"; they say that such ill effects occur chiefly, if not wholly, in cases in which the ether has been unduly and unnecessarily pushed. Kemp (quoted by Hewitt<sup>4</sup>) says that ether causes a special contraction of the arterioles of the kidney, with decreased secretion of urine. He believes that it gives rise to a damaged state of the secreting cells and that albumin appears early in the urine secreted.

Regarding the purely psychic effect of the ordeal of preparing for operation and taking the anesthetic, the following quotation from Crile<sup>5</sup> is of interest:

We now know that fear alone may cause physical damage, not alone to the brain, but to other organs. It causes an increase in adrenalin, in the output of glycogen, and in rabbits repeatedly frightened, albumin and casts are sometimes produced.

3. Bovée: Renal Excretion During the Administration of Chloroform and Ether in Gynecological Surgical Operations, Tr. New York Obst. Soc., Am. Jour. Obst., 1909, lix, 1004.

4. Hewitt: Anesthesia, Ed. 4, 1912, p. 383.

5. Crile: Nitrous Oxide Anaesthesia, with Note on Anoci-Association, a New Principle in Operative Surgery, Surg., Gynec. and Obst., 1911, xiii, 170.



Von Brunn<sup>6</sup> says that in deep anesthesia the urine is decreased in amount, though occasionally it may show increase, and that for two or three days there is an increase in the specific gravity. The loss of function of the renal parenchyma apparently corresponds to the length of the anæsthesia (compare our cases below). He says that ether may, if given several times within twenty-four hours, cause fatty degeneration and necrosis of tissues in animals. He has collected figures from various authors, taking into consideration the occurrence of albumin before as well as after operation, and these will be stated in part:

	Albumin Before	Albumin After
Roux—		
119 cases ether .....	4	4
Butter—		
500 cases ether .....	0	1
Wunderlich—		
72 cases ether .....	0	6
52 cases chloroform .....	0	6
1 case chlor-ether .....	0	1
Eisendrath—		
60 cases ether .....	25.0 per cent. showed albumin afterward	
70 cases chloroform.....	32.0 per cent. showed albumin afterward	
Deaver and Frese—		
63 cases ether .....	47.6 per cent. showed albumin afterward	

Von Brunn says:

It must be said that ether may cause trouble with the kidney, which may manifest itself by irregularities of excretion, decreased nitrogen excretion, albuminuria and cylindruria. These, however, are only of a fleeting nature, and occur, at least so far as albumin and casts go, in only a small percentage of the cases. A preëxisting albuminuria or cylindruria may be increased by ether narcoses. Compared with chloroform, ether is less dangerous.

In nephritis, general narcosis should be avoided if possible—if it cannot be avoided, ether is better than chloroform.

Popoff<sup>7</sup> reported 140 cases of patients examined before and after ether. Of these 140 cases, 14 showed albumin before operation and 28 afterward—in other words, 10 per cent. had albuminuria as a result of operation under ether. Konwer (quoted by Popoff<sup>7</sup>) reports 100 cases of which 5 showed postoperative albuminuria. Popoff concluded that ether may cause transient albuminuria, that it may cause or increase casts, but that nevertheless the general condition of a patient is never made worse by it. Buxton,<sup>8</sup> as a result of his investigations, states that:

In most cases the quantity of the urinary water was reduced, but probably not more so than could be accounted for by the abstinence from food and liquids. The solids remained practically unaffected. When ether is given in

6. Brunn, M. V.: Die Allgemeinnarkose, Tübingen, 1913, p. 171.

7. Popoff, Wassil: Contributions à l'étude de l'albuminurie après l'éthérisation, Thèse Inaugurale, Genève, 1896.

8. Buxton: Anaesthetics, Philadelphia, 1907, pp. 47, 120.

excessive quantity, ischemia of the kidneys is produced and albuminuria results. If, however, only so much is inhaled as is needed for complete anesthesia, no deleterious effects arise, and the renal parenchyma is not injured nor does albuminuria result. The experimental work was supplemented by the study of clinical cases and these bore out our experimental deductions.

Later he says:

In renal disease, when extensive, ether is said to induce suppression of urine, so that if given at all in these cases it should be used with caution.

Blake<sup>9</sup> gives figures collected by other authors concerning death from anesthesia, and those are interesting in this connection:

Gurli—

166,812 chloroform cases, 63 deaths.....	1 in 2,647
26,320 ether cases, 2 deaths.....	1 in 13,160
8,014 ether and chloroform, 1 death.....	1 in 8,014
Zeigler, 600 ether cases.....	No deaths
Tschmarke, 500 ether cases.....	No deaths
Körte, 600 ether cases.....	No deaths
Vogel, 1,200 ether cases.....	Two deaths or serious complications
Ollier, 40,000 ether cases.....	No deaths
Chalot, 730 ether cases.....	No deaths
Tillier, 6,500 ether cases.....	No deaths
Poucet, 15,000 ether cases.....	No deaths

Juillard—

314,738 ether cases, 21 deaths.....	1 in 14,987
524,507 chloroform cases, 161 deaths.....	1 in 3,258

Blake examined personally 50 cases before and after ether; of these, 17 showed albumin before, and in 11 of these 17, the albumin was increased. Of the 33 with no albumin before operation, 25 showed it afterward. These figures are much higher than those of most other observers. Blake believes that the albuminuria is due to a passing irritation of the kidney and not to a true nephritis.

J. Wyllis Hassler,<sup>10</sup> speaking in regard to the urine after intravenous anesthesia, says:

The urinary analysis made before the operation and for three or four days afterward showed no marked difference in the specimens. The total amount was increased and the specific gravity lowered in the first twenty-four hours; often the specific gravity and solid content of the urine remained unchanged. In no case, even after the employment of a 7.5 ether solution, did blood, albumin or casts appear in the urine, though German observers did report occasional cases of transient hemoglobinuria after the use of the stronger ether mixtures.

There are countless articles in the literature dealing with one or another of the dangers of anesthetics and how to avoid these dangers, but as the great majority have no direct bearing on the subject in hand, no further reference will be made to them.

9. Blake, J. B.: An Examination of Some Recent Statistics in Regard to Ether, and a Consideration of Some Present Methods of Its Administration, Boston Med. and Surg. Jour., 1895, cxxxii, 559.

10. Hassler: Intravenous Anaesthesia, Ann. Surg., 1913, lviii, 900.

## AUTHORS' WORK

Our work was done on the ward cases at the Massachusetts General Hospital, the patients being taken without regard to age, general condition, or the specific nature of their ailment. A desire for as much accuracy as possible made it seem wise to avoid, to a certain extent, such nephrectomies and nephrotomies as would have, after operation, an excess of blood in the urine, and the prostatectomies, in which the constant irrigation after operation, plus the blood, made careful work well-nigh impossible. Also it was found impossible to use stricture cases on account of the difficulty of getting the urine before operation. After early experiences in the work, attempts to carry through the test on female patients were given up on account of the unavoidable difficulty encountered in getting them catheterized at the proper time after operation. This was not due in the least to any unwillingness on the part of the attendants, but to other duties which continually presented themselves and which were clearly too important to neglect. The collection of the urine at the end of the two-hour period was done personally, as it was early found that this was the only way to be sure of having it done completely and at the proper time.

The great majority of the patients were tested on the day of their entrance into the hospital—only a small number being tested after they had been in the wards one or more days. Whether the fact that most of the patients were more or less frightened over their new surroundings and anticipations of future operation could have any reflex inhibitory effect on their visceral functions and more particularly on their kidney function, as shown by phenolsulphonephthalein, would be in most cases, difficult to state—though such a possibility does not seem beyond the realms of reason (see Crile<sup>5</sup> quoted above).

Each patient was directed to empty his bladder and was then given 1 c.c. of phenolsulphonephthalein into the muscles of the thigh. Injections into the lumbar muscles were given up early on account of the difficulty encountered in attempting to give the injection in the same place after the operation. The patients were questioned as to the frequency of micturition, nocturia, etc., and those in whom was no history suggesting retention and residual urine emptied their bladders by voiding at the end of two hours from the time of injection. In only a very few cases did catheterization seem necessary at this time, but as will later be pointed out, certain discrepancies in some of the results are most probably due to the fact that the patient really did not completely empty his bladder, though he seemed to at the time. The drug was given with a 3 c.c. Paris glass syringe, the plunger being drawn up to the mark 1.1 c.c., then driven in to the mark 0.1 c.c., thus obviating any error from injecting bubbles of air, which would otherwise occasionally happen.

The second injections were given at various times — in some cases just at the beginning of the operation, and in others at different periods after the end of the operation — some being a day or more later. At the end of the two-hour period, if the patient was perfectly conscious and could void without difficulty, he was allowed to do so, but in the majority of cases the catheter was necessary. All the ordinary aseptic precautions were taken in catheterizing, and to the best of our knowledge in no case was the bladder or urethra infected. Also, no patient was infected from the injecting needle, though occasionally a patient would complain for a day or two of a stiff, sore thigh. In catheterizing patients who were still under ether, or only partly out of its influence, a large number were found to have a profuse secretion of mucus from the urethra, in many cases almost enough to lubricate the catheter. This secretion was observed in almost every case in which the foreskin covered the glans; in the other cases it undoubtedly was present, but was wiped away as the patient moved about in bed. This seems to prove that ether causes the secretion of mucus from the urethral mucous membrane, and not improbably from all the mucous membranes of the body, though usually its effect is apparent only in the upper air passages and membranes which come in direct contact with the ether vapor.

The attempt was always made to make the collection at the end of exactly two hours, but an error of a very few minutes — practically never over five minutes — was frequently unavoidable, owing to various factors, but it did not seem to us that an error so small as that would make any material difference in the results.

The two-hour specimen was measured for the amount, and the reaction noted; it was then made alkaline with 33 per cent. potassium hydroxid and diluted to 1 liter and filtered. It was then compared in the Duboscq colorimeter with a standard solution of 3.0 mg. phenolsulphonephthalein to the liter of water, and made slightly alkaline. In practically none of the cases was the urinary pigment abundant enough to cause doubt as to the accuracy of the reading. In a few cases in which there was considerable blood we found one fairly satisfactory method was to let the specimen stand over night, at the end of which time most of the blood would be settled at the bottom of the flask, the overlying urine being fairly clear and only slightly stained with blood pigment. Part of this clear urine was decanted off and examined, and then the total phenolsulphonephthalein content estimated by measuring the two portions and figuring out how much would be contained in the rest of the urine in the flask. This seems to be a reasonably efficient method. In one case in which there was an excess

of bile in all specimens, the urine obtained before operation was used as a standard with which to compare that obtained afterward, and in this way a fairly accurate comparison could be made. For a long time artificial light was not used, but toward the end of the work it was discovered that the readings made by electric light were always the same as those made by daylight, and thereafter there was no hesitation about doing the readings by electricity. (The feasibility of this use of artificial light is agreed to by Dr. Palmer of the chemical laboratory at the hospital.)

Coming to the actual results of the work, it is of interest first to consider the average output of the patients just as they came to the hospital, and before operation. No account is taken in these figures of the patient's condition or that of his kidneys, though in the great majority of the cases the kidneys were normal. These figures also do not include a few cases, which will be referred to next, in which more than one test was done, but there was no operation. There were 422 such cases with an average output in two hours of 58.5 per cent. This figure is lower than that of Rowntree and Geraghty,<sup>11</sup> who state that the normal is from 60 to 80 per cent., but they measure from the time of appearance, and not from the time of injection, as in this case. On the other hand, this is higher than that of Keyes and Stevens,<sup>12</sup> who get an average normal output, in two hours from the time of appearance, of only 57.2 per cent. In this series the highest total for the two hours was 94.0 per cent., and the lowest 00.0 per cent. The latter was in the case of a much-emaciated and cachectic woman with inoperable carcinoma of the cervix uteri. She failed to excrete any of the drug in two hours after a subcutaneous injection, and the following day failed to excrete any in one hour following intramuscular injection. She subsequently went through an operation under gas and oxygen for cautery of the growth, and then was lost sight of. One urinalysis was as follows:

Pale, turbid, acid, 1.010; albumen, trace; sugar, 0; sediment, much pus.  
and two days later:

Milky, acid, 1.014; albumin, very large trace; sugar, 0; sediment, much pus.  
She survived the operation and left the hospital. She has undoubtedly died of cancer before now, if not from renal insufficiency.

11. Rowntree and Geraghty: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein. *Jour. Pharmacol. and Exper. Therap.*, 1910, 1, 579.

12. Keyes and Stevens: A Clinical Study of Renal Function by Means of Phenolsulphonephthalein, *Am. Jour. Urol.*, 1911, vii, 367.

Of the above-mentioned 422 cases, 409 were next classed into four groups according to ages, as follows:

- Group 1, age, 1-19, inclusive
- Group 2, age, 20-39, inclusive
- Group 3, age, 40-59, inclusive
- Group 4, age, 60-., inclusive

Their output was then estimated according to these groups, and in spite of the fact that, as noted above, no account is taken of their condition, the results are interesting:

Group 1, age 1-19, 46 cases.

Lowest, 27.0 per cent.; highest, 90.9; average, 67.8 per cent.

Group 2, age 30-39, 173 cases.

Lowest, 20.0 per cent.; highest, 92.6 per cent.; average, 62.2 per cent.

Group 3, age 40-59, 154 cases.

Lowest, 00.0 per cent.; highest, 80.5 per cent.; average, 56.8 per cent.

Group 4, age 60, 36 cases.

Lowest, 5.0 per cent.; highest, 82.5 per cent.; average, 45.7 per cent.

To put it more concisely:

Age 1-19, average phenolsulphonephthalein, 67.8 per cent.

Age 20-39, average phenolsulphonephthalein, 62.2 per cent.

Age 40-59, average phenolsulphonephthalein, 56.8 per cent.

Age 60 ., average phenolsulphonephthalein, 45.7 per cent.

These figures illustrate rather strikingly what one might be led to expect, namely, that the kidney function, as demonstrated by the excretion of phenolsulphonephthalein, becomes progressively less as one grows older.

Before taking up variations in function following anesthesia, it is of interest to consider a few cases in which the functional test was performed more than once on the same patient, without operation. This will give an idea of how much fluctuation in the test one may expect under ordinary circumstances. A few cases taken from other authors will first be mentioned:

Rowntree and Geraghty.<sup>13</sup>

Intravenous injection, output in one hour:

- Case 5, Test 1, 62.5 per cent.
- Test 2, 62.5 per cent.
- Test 3, 63.3 per cent.
- Case 10, Test 1, 64.5 per cent.
- Test 2, 72.7 per cent.
- Case 12, Test 1, 62.5 per cent.
- Test 2, 65.8 per cent.
- Test 3, 65.5 per cent.
- Case 14, Test 1, 71.5 per cent.
- Test 2, 68.5 per cent.

13. Rowntree, L. G., and Geraghty, J. T.: The Phthalein Test, *THE ARCHIVES INT. MED.*, 1912, ix, 284.



Lumbar injection, one-hour excretion:

Case 6,	Test 1,	54.0 per cent.
	Test 2,	54.3 per cent.
Case 10,	Test 1,	40.2 per cent.
	Test 2,	60.9 per cent.
	Test 3,	60.2 per cent.
	Test 4,	60.2 per cent.
Case 11,	Test 1,	61.7 per cent.
	Test 2,	64.1 per cent.
	Test 3,	63.2 per cent.
Case 13,	Test 1,	62.5 per cent.
	Test 2,	62.5 per cent.

Cases of Keyes and Stevens.

Comparison of excretion on different days:

CASE 1.—Syphilis of spinal cord:

Test 1: Appear. time, 8 minutes, two-hour excretion, 71.2 per cent.  
 Test 2: Appear. time, 9 minutes, two-hour excretion, 56.0 per cent.

No change of condition clinically.

CASE 2.—Hypospadias:

Test 1: Two-hour excretion, 56.0 per cent.  
 Test 2: Two-hour excretion, 49.4 per cent.  
 Test 3: Two-hour excretion, 61.8 per cent.  
 Test 4: Two-hour excretion, 56.0 per cent. (intravenous)

CASE 3.—Gonorrheal epididymitis:

Test 1: Two-hour excretion, 54.6 per cent.  
 Test 2: Two-hour excretion, 53.+ per cent.

Personal cases:

CASE 1.—Man, aged 69, extensive rodent ulcer of face:

Test 1: April 30, 1913, two-hour excretion, 44.4 per cent.  
 Test 2: Aug. 12, 1913, two-hour excretion, 40.3 per cent.

CASE 2 (No. 320).—Two tests done in the interval between an exploratory laparotomy and a later colostomy for cancer:

Test 1: July 2, 1913, two-hour excretion, 32.1 per cent.  
 Test 2: July 4, 1913, two-hour excretion, 33.3 per cent.

CASE 3 (No. 349).—Man, aged 56; cancer of jaw:

Test 1: Two-hour excretion, 59.5 per cent.  
 Test 2: Two-hour excretion, 62.5 per cent.

CASE 4.—Man; fracture of patella:

Test 1: Aug. 13, 1913, two-hour excretion, 71.4 per cent.  
 Test 2: Oct. 24, 1913, two-hour excretion, 67.5 per cent.

CASE 5.—Man, aged 56; cancer of jaw; patient in poor condition:

Test 1: Sept. 17, 1913, two-hour excretion, 31.6 per cent.  
 Test 2: Sept. 20, 1913, two-hour excretion, 32.2 per cent.

CASE 6.—Man; cancer of thyroid:

Test 1: October 7, two-hour excretion, 82.5 per cent.

This patient left the hospital and came back weak and emaciated, almost starved.

Test 2: November 6, two-hour excretion, 44.4 per cent.

In this case the change in the patient's condition might account for the decreased output.

CASE 7.—Man, aged 31. Between the two following tests the patient was prepared for operation, given two enemas, and on the 21st starved up to the time of test:

Test 1: June 20, 1913, two-hour excretion, 54.9 per cent.  
 Test 2: June 21, 1913, two-hour excretion, 39.0 per cent.

CASE 8.—Boy, aged 15; hernia. At the time of the first test this patient had bronchitis, because of which he was discharged without operation:

Test 1: March 18, two-hour excretion, 60.2 per cent.  
 Test 2: June 9, two-hour excretion, 79.3 per cent.

CASE 9.—A strong man, aged 28, in perfect health. The test was done at the same time each afternoon, but conditions had varied during the morning's work:

Test 1:	June 10,	two-hour excretion,	81.9 per cent.
Test 2:	June 11,	two-hour excretion,	71.4 per cent.
Test 3:	June 12,	two-hour excretion,	70.4 per cent.
Test 4:	June 14,	two-hour excretion,	76.9 per cent.
Test 5:	June 15,	two-hour excretion,	79.3 per cent.
Test 6:	June 16,	two-hour excretion,	70.4 per cent.
Test 7:	June 17,	two-hour excretion,	79.3 per cent.
Test 8:	July 1,	two-hour excretion,	71.4 per cent.*
Test 9:	July 4,	two-hour excretion,	82.5 per cent.
Test 10:	July 6,	two-hour excretion,	73.5 per cent.*

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\* Perspiring profusely.

These cases have been given in detail to show what fluctuation may be encountered, normally or abnormally. In certain of the foregoing there seems to be a definite reason for changes in the output, as in Case 6 of the authors. The figures of Rowntree and Geraghty are most consistent, though they have one variation of 20.7 and another of 8.20. Perhaps the most instructive figures are those of the last case, in which ten tests were done on a normal man, with results varying from 70.4 per cent. to 82.5 per cent. It seems that it would be a very difficult thing to name any limits which we could call normal for any given case.

#### GENERAL AVERAGES BEFORE AND AFTER ETHER

These are the figures of 335 cases in which tests were performed on the entrance to the hospital and again after an operation under ether, with or without such accessories as nitrous oxid, anesthol (a mixture of ether, chloroform and ethyl chlorid), local anesthesia, etc. As will be noted later, not all the cases showed a decreased output of phenolsulphonephthalein, but they are included among these figures:

Number of cases, 335.

Average excretion, before operation, 59.3 per cent.

Average excretion, after operation, 48.1 per cent.

Difference ..... 11.2 per cent.

Decrease, 18.8 per cent. of average output before.

These are general figures, not taking into consideration the nature of the operation, the time of injection of the drug, or the condition of the patient.

#### GENERAL AVERAGES BEFORE AND AFTER SPINAL ANESTHESIA

In this series there are not enough cases to prove of much value, but they are inserted here for what they are worth:

Number of cases, 16.

Excretion before operation, 49.7 per cent.

Excretion after operation, 41.4 per cent.

Difference ..... 8.3 per cent.

Decrease of 16.7 per cent. of average output before.

In spite of the few cases at hand, it is interesting that the decrease in phenolsulphonephthalein output is not so great as that after ether (18.8 per cent.).

#### LOCAL ANESTHESIA

The same may be said here as was noted in regard to the spinal anesthesia; there are only eight cases, which are interesting even if not of much value:

Number of cases, 8.	
Excretion before operation,	50.8 per cent.
Excretion after operation,	44.7 per cent.
	<hr/>
Difference .....	6.1 per cent.
Decrease, 12.0 per cent. of output before.	

Here again it will be noted that though few in number they show less decrease than the ether cases.

#### GAS AND OXYGEN

There were only nine such cases which we were able to test fully, and the results are given below, though they do not coincide with our theory as to what they should be. It would seem natural to expect the kidneys to show little or no effect after this anesthesia, whereas our few cases show even more decrease in output than after ether. A much larger number must be examined before any conclusions can be rightly drawn. These figures, therefore, are added only for what they may be worth:

Number of cases, 9.	
Output before operation,	59.7 per cent.
Output after operation,	44.3 per cent.
	<hr/>
Difference .....	15.4 per cent.
Decrease, 25.7 per cent. of output before operation.	

#### FURTHER ANALYSIS OF THE ETHER CASES

It next seemed wise to analyze the results after ether, according to the time of administration of the drug in its relation to the anesthesia. The cases are grouped into eight classes, as will be noted below, and then the general averages of each group, before and after operation, compared. Throughout this paper it will be observed that the actual difference in percentage of phenolsulphonephthalein excreted before and after operation is not taken as the "percentage of decrease"; to obtain this latter the actual number of points decrease is divided by the output before operation. The results shown by the following figures are striking in that they show a very distinct relation between the time of injection and the output of the drug.

## 1. Injection just before or during operation:

Number of cases, 16.

Output before operation, 61.7 per cent.

Output after operation, 46.2 per cent.

Difference ..... 15.5 per cent.

Decrease in output, 25.1 per cent.

## 2. Injection within one hour of end of anesthesia:

Number of cases, 8.

Output before operation, 63.4 per cent.

Output after operation, 47.8 per cent.

Difference ..... 15.6 per cent.

Decrease in output, 24.7 per cent.

## 3. Injection between one and two hours after anesthesia:

Number of cases, 24.

Output before operation, 65.6 per cent.

Output after operation, 52.0 per cent.

Difference ..... 13.6 per cent.

Decrease in output, 20.9 per cent.

## 4. Injection between two and four hours after anesthesia:

Number of cases, 125.

Output before operation, 60.2 per cent.

Output after operation, 48.0 per cent.

Difference ..... 12.2 per cent.

Decrease in output, 20.2 per cent.

## 5. Injection between four and six hours after anesthesia:

Number of cases, 94.

Output before operation, 58.7 per cent.

Output after operation, 47.3 per cent.

Difference ..... 11.4 per cent.

Decrease in output, 19.4 per cent.

## 6. Injection between six and twelve hours after anesthesia:

Number of cases, 21.

Output before operation, 63.2 per cent.

Output after operation, 52.0 per cent.

Difference ..... 11.2 per cent.

Decrease in output, 17.7 per cent.

## 7. Injection between twelve and twenty-four hours after anesthesia:

Number of cases, 12.

Output before operation, 55.3 per cent.

Output after operation, 51.4 per cent.

Difference ..... 3.9 per cent.

Decrease in output, 7.0 per cent.

## 8. Injection between twenty-four and forty-eight hours after anesthesia:

Number of cases, 25.

Output before operation, 59.2 per cent.

Output after operation, 57.0 per cent.

Difference ..... 2.2 per cent.

Decrease in output, 3.7 per cent.

These figures seem to demonstrate that the output of phenolsulphonephthalein is affected most during or soon after operation, and returns to approximately normal in forty-eight hours.

Though the amount of ether used in an operation is by no means always indicative of the state of narcosis of the patient, it was decided to study the cases from this point of view also, though in a good many of the whole series the amount of ether could not be ascertained, and at best it is only approximate. In all of these cases the test was done within six hours of the end of the operation.

1. Amount of ether, 1-4 oz.

Number of cases, 1.

Output before operation, 55.5 per cent.  
Output after operation, 50.0 per cent.

Difference ..... 5.5 per cent.

Decrease in output, 9.9 per cent.

2. Amount of ether, 4-12 oz.

Number of cases, 161.

Output before operation, 59.8 per cent.  
Output after operation, 49.1 per cent.

Difference ..... 10.7 per cent.

Decrease in output, 17.8 per cent.

3. Amount of ether, 12-20 oz.

Number of cases, 73.

Output before operation, 61.2 per cent.  
Output after operation, 45.8 per cent.

Difference ..... 15.4 per cent.

Decrease in output, 25.1 per cent.

4. Amount of ether, 20 oz. or more:

Number of cases, 17.

Output before operation, 60.4 per cent.  
Output after operation, 44.5 per cent.

Difference ..... 15.9 per cent.

Decrease in output, 26.3 per cent.

These results are interesting and instructive, and if they may be depended on, they show clearly that the effect on the kidney, as shown by phenolsulphonaphthalein, is directly dependent on the amount of ether used. These figures are probably the least reliable of any, on account of the difficulty of knowing accurately the amount of ether the patient actually gets.

The ether cases were again interpreted to show the effect of the duration of the operation and the anesthesia. They are divided into three groups, and in every case the second test was done within six hours of the end of the operation.

1. Length of anesthesia, one hour or under:

Number of cases, 151.

Output before operation, 61.1 per cent.  
Output after operation, 50.3 per cent.

Difference ..... 10.8 per cent.

Decrease in output, 17.6 per cent.

2. Length of anesthesia, from one to two hours:  
 Number of cases, 95.  
     Output before operation, 60.8 per cent.  
     Output after operation, 46.3 per cent.  
     Difference ..... 14.5 per cent.  
 Decrease in output, 23.8 per cent.
3. Length of anesthesia, over two hours:  
 Number of cases, 14.  
     Output before operation, 52.2 per cent.  
     Output after operation, 38.5 per cent.  
     Difference ..... 13.7 per cent.  
 Decrease in output, 26.2 per cent.

SUMMARY		
Duration	No. Cases	Decrease % Phthalein
0-1 hr.	151	17.6
1-2 hrs.	95	23.8
2 hrs.	14	26.2

Here is another fairly striking result — that the length of the operation and anesthesia bears a definite relation to the postoperative excretion of phenolsulphonephthalein.

#### CASES SHOWING INCREASED EXCRETION OF PHENOLSULPHONE- PHTHALEIN AFTER OPERATION

Of the complete series, eighty-four cases showed a higher output after operation than before. It seems significant that, in spite of the fact, the general trend of results after operation is consistently downward. It appears that most of these cases can be explained in such a way as not to change one's convictions as obtained from the general averages. A more careful study of these eighty-four cases shows that:

1. Forty-nine out of the eighty-four cases showed an increase of less than 10 points. If it be assumed, from figures given above under the heading of normal variations in renal function, that the output may vary from day to day, then it may be said that the majority of these cases which show increased phenolsulphonephthalein output have not been actually stimulated to increased work, but rather have not been affected one way or another by the anesthesia and the operation. If this be agreed for cases showing slight increase, the same would have to be said for all those cases showing a similar amount of decrease.

2. In four of the cases, to wit., (a) subdiaphragmatic abscess, (b) empyema, (c) lung abscess and (d) reduction of a painful fracture, the patient's mental or psychic condition was greatly relieved, as well as his suffering, and this might tend to aid his renal function.

3. In eight of the cases the tests were done over twenty-four hours after the operation.



4. One was a case of gas-oxygen anesthesia.
5. Two were cases of local anesthesia.
6. Five were cases of spinal anesthesia.

7. In ten of the cases the results were such as to suggest strongly a possible error, in that it seemed probable that the bladder was not completely emptied at the time of the first test. This may occasionally have been true of some of the others, but there was nothing about them, save the results, to suggest that such might have been the case.

As examples of these cases of increase which are hard to explain, we cite three:

CASE 1.—Man, aged 50; rodent ulcer of face; No. 164.

Test: May 16; 1 c.c. phthalein; voided in two hours. Urine, 145 c.c.; phthalein, 25.0 per cent.

Operation: May 17, gas-ether, 9 ounces; duration thirty-five minutes. Excision of rodent ulcer.

Test: May 17, three hours after close of operation: 1 c.c. phthalein; voided in two hours. Urine, 325 c.c.; phthalein, 42.7 per cent.

CASE 2.—Man, aged 20; No. 65.

Test: January 7, 1 c.c. phthalein; voided in two hours. Urine, 390 c.c.; phthalein, 41.6 per cent.

Operation: January 9, gas-ether, 13 ounces. Duration, half an hour. Appendectomy.

Test: January 9, 1 c.c. phthalein, three hours and forty minutes after operation. Catheterized in two hours. Urine, 300 c.c.; phthalein, 68.4 per cent.

CASE 3.—Man, aged 34; No. 310.

Test: June 25, 1 c.c. phthalein, voided in two hours. Urine, 190 c.c.; phthalein, 36.2 per cent.

Operation: June 26, gas-ether, 10 ounces. Duration, one hour and fifty minutes. Gastro-enterostomy.

Test: June 26, 1 c.c. phthalein, four hours and thirty-eight minutes after operation; catheterized. Urine, 210 c.c.; phthalein, 67.5 per cent.

On the other hand, in contrast to these one sees a few cases in which, without any evident reason, the phenolsulphonephthalein output after operation goes down practically to zero, and that in cases of strong rugged men who have undergone operations neither long or serious. We quote a few of these as examples:

CASE 1.—Boy, aged 19; general health excellent; No. 416.

Test: November 3, 1 c.c. phthalein, voided in two hours. Urine, 125 c.c.; phthalein, 52.6 per cent.

Operation: November 4, gas-ether, 5 ounces. Duration, thirty minutes. Appendectomy.

Test: November 4, 1 c.c. phthalein, two hours and forty-five minutes after operation; catheterized in two hours. Urine, 85 c.c.; phthalein, 16.6 per cent.

CASE 2.—Young man, aged 18, well developed and nourished.

Test: May 19, 1 c.c. phthalein, voided in two hours. Urine, 130 c.c.; phthalein, 76.9 per cent.

Operation: May 20, gas-ether, 4 ounces. Duration, twenty-five minutes. Incision and drainage submaxillary abscess.

Test: May 20, 1 c.c. phthalein, two hours and twenty minutes after operation. Catheterized in two hours. Urine, 200 c.c.; phthalein, 15 per cent.

CASE 3.—Young man, aged 18, well developed and nourished.

Test: May 12, 1 c.c. phthalein; voided in two hours. Urine, 160 c.c.; phthalein, 76.9 per cent.

Operation: May 13, ether, 6 ounces. Duration, forty-five minutes. Radical cure inguinal hernia.

Test: May 13, 1 c.c. phthalein, forty-five minutes after operation. Catheterized in two hours. Urine, 115 c.c.; phthalein, too low to estimate accurately, about 10 per cent.

CASE 4.—Man, aged 37; well developed and nourished.

Test: April 23, 1 c.c. phthalein; voided in two hours. Urine, 675 c.c.; phthalein, 70.4 per cent.

Operation: April 24, gas-ether, 18 ounces. Duration, one hour and five minutes. Appendectomy.

Test: April 24, 1 c.c. phthalein, two hours and fifty minutes after operation. Catheterized in two hours. Urine, 170 c.c.; phthalein, approximately 7.5 per cent.

No one of these patients had a very long or shocking operation; they were all fairly young and healthy, and there seems no reason to doubt the accuracy of the results. Contrast with these:

CASE 1.—Man, aged 24; well developed and nourished; No. 357.

Test: October 22, 1 c.c. phthalein; voided in two hours. Urine, 250 c.c.; phthalein, 62.5 per cent.

Operation: October 23, gas-ether, 15 ounces. Duration one hour and twenty minutes. Appendectomy; exploration.

Test: October 23; patient unconscious; 1 c.c. phthalein, one hour and ten minutes after end of operation. Catheterized in two hours. Urine, 80 c.c.; phthalein, 62.5 per cent. No change.

CASE 2.—Man, aged 41; well developed and nourished.

Test: July 11, 1 c.c. phthalein, voided in two hours. Urine, 250 c.c.; phthalein, 52.6 per cent.

Operation: July 12, gas-ether, 14 ounces. Duration, 40 minutes.

Test: July 12, 1 c.c. phthalein, two hours and twenty minutes after operation. Voided in two hours. Urine, 120 c.c.; phthalein, 52.6 per cent. No change.

CASE 3.—Man, aged 29; well developed and nourished.

Test: August 1, 1 c.c. phthalein; voided in two hours. Urine, 990 c.c.; phthalein, 58.1 per cent.

Operation: August 2, gas-ether, 6 ounces. Duration, 55 minutes. Clamp and cautery for hemorrhoids.

Test: August 2, patient partly out of ether; 1 c.c. phthalein, one hour and twenty minutes after operation. Catheterized in two hours. Urine, 120 c.c.; phthalein, 57.0 per cent. Decrease, 1.8 per cent.

All the foregoing cases were picked out as examples of three types — those showing marked increase, those showing marked decrease and those showing practically no change at all. And in these particular cases, especially those of the first two groups, there is no adequate explanation of the results — just why there was so much increase or so much decrease is hard to say. They tend to confuse one a good deal, and on studying them, with the general averages above in mind, it seems a fair presumption to explain them on the ground of the personal idiosyncrasy of the patient to ether, just as is seen in the reaction of certain individuals to other drugs.

## EFFECT OF SHOCK

Cases of pure shock were much desired for this work, but were very hard to get, as almost every patient was either operated on at once, or else died in a few hours without operation. Only one such case of value came in, and it will be given in detail, as it was very interesting:

CASE 1.—Italian, aged 40, well developed and nourished. September 24, brought to the hospital with fractured femur, fractured ribs, fractured fibula and compound fracture of tibia. Patient in such severe shock that he was left on shock table and later put to bed in ward.

Test: 1 c.c. phthalein; catheterized in two hours. Urine, 215 c.c.; phthalein, approximately 5.0 per cent.

September 25: Fractures reduced under ether.

October 7: Patient in good condition, convalescing.

Test: 1 c.c. phthalein; voided in two hours. Urine, 105 c.c.; phthalein, 58.1 per cent.

This is a striking case, and though the only one of its kind, seems to show that shock *per se* has a great inhibitory action on kidney function (cf. Crile's work on shock). Under this heading the following cases are of interest, though they do not present shock alone.

CASE 2.—Man, aged 56; brain abscess; very sick.

Test: October 8, 1 c.c. phthalein; catheterized in two hours. Urine, 75 c.c.; phthalein, 67.5 per cent.

Operation: October 16, gas-ether, 10 ounces. Duration, one hour and fifteen minutes. Craniotomy for brain abscess.

Test: October 16, patient partly out of ether. In shock and on dangerous list. One c.c. phthalein, 5 hours and 55 minutes after operation. Catheterized in two hours. Urine, 90 c.c.; phthalein, 15.0 per cent.

CASE 3.—Man, aged 35, poorly nourished; osteomyelitis of femur.

Test: October 28, 1 c.c. phthalein; voided in two hours. Urine, 110 c.c.; phthalein, 86.2 per cent.

Operation: October 29, spinal anesthesia; hip-joint amputation.

Test: October 29, patient in poor condition and on dangerous list. One c.c. phthalein, seven hours and ten minutes after operation. Catheterized in two hours. Urine, 75 c.c.; phthalein, 26.0 per cent.

Theoretically, there should not be shock during or after an operation under spinal anesthesia, but the patient's condition was such as to suggest that the effect of the anesthetic had worn off and that at the time of the test he was actually in a state of shock—and that the shock and not the anesthetic was the cause of the great decrease in phthalein output.

CASE 4.—Man, aged 40. Fairly nourished. Cancer of rectum.

Test: February 19, 1 c.c. phthalein; voided in two hours. Urine, 90 c.c.; phthalein, 54.3 per cent.

Operation: February 25, spinal plus ether. Combined abdominal and perineal operation for cancer of rectum.

Test: February 25, patient in very severe shock and unconscious. One c.c. phthalein three hours after operation. Catheterized in two hours. Urine, 65 c.c.; phthalein, 00.0 per cent.

It seems here that the shock and not the anesthetic is responsible.

Test: February 26, day after operation, 1 c.c. phthalein; phthalein excretion, 50.0 per cent.

This demonstrated the rapid return to the normal, or to nearly normal.

The following case is not one of shock, though the patient was on the dangerous list at the time of the second test, and died shortly after.

CASE 5.—Man, aged 47, brain tumor.

Test: May 26, 1 c.c. phthalein, voided in two hours. Urine, 90 c.c.; phthalein, 80.5 per cent.

Operation: May 31, ether 10 ounces. Duration, two hours. Craniotomy for brain tumor.

Test: June 2, two days after operation. Patient semiconscious. One c.c.

The foregoing cases have been cited to illustrate what seems to be a very probable fact, namely, that the general condition of the patients, leaving the anesthetic entirely out of the question, and where there is also no kidney lesion, must have some influence on the amount of phenolsulphonephthalein excreted. In Case 1 above, there was no local kidney injury; the surgical shock alone must account for the low output, and, granted this, it is difficult to differentiate in Cases 2, 3 and 4 between the effect of the anesthetic and the effect of the patient's reduced vitality and low ebb of life — at the time. In Case 5 the test was done so long after the operation that neither the anesthetic nor surgical shock could be considered as of any moment, and here again the factor is the poor general condition and what turned out to be impending death.

#### KIDNEY CHANGES AS SHOWN BY URINALYSIS

Of all the cases in this series, 208 had complete urinalysis before and after operation. These examinations were not made from the same specimens which were used for the determination of the phenolsulphonephthalein excretion, as it was deemed best to use these entire, for the sake of greater accuracy. Of these 208 cases, twenty-two, or 10.5 per cent., showed after operation either the presence of albumin when it has been absent before, or else an increase in the amount of preexisting albumin. In this list are not included cases of operation on the genito-urinary tract, in which the sequelae of operation, blood and pus in the urine, would naturally give rise to the presence of albumin. Of the twenty-two cases, seventeen were ones in which albumin appeared when it had been absent before, and five were cases of increase. Compared with the figures given at the beginning of this paper, this percentage of 10.5 is neither high nor low — it falls between the extreme figures of the different authors.

The changes in phenolsulphonephthalein output after operation in these twenty-two cases are briefly as follows:

- Two showed no change.
- Three showed decreased output of 5 per cent. or under.
- Three showed decreased output of 5-10 per cent.
- Four showed decreased output of 10-20 per cent.
- Five showed decreased output of 20-40 per cent.
- Five showed increased output.

In view of these results, it seems that the presence of or absence of albumin after operation, bears no definite relation to the increased or decreased output of phenolsulphonephthalein after operation. Also, there were in these cases, sixty-three which showed a decrease in phenolsulphonephthalein output after operation of over twenty points, in which cases the postoperative urine was normal with no albumin. The albuminuria does not go *pari passu* with the decreased excretion of phenolsulphonephthalein.

#### THE IMPROVEMENT OF RENAL FUNCTION AFTER IT HAS ONCE DROPPED

The figures given above to illustrate the variations in phenolsulphonephthalein output according to the time after operation at which the test is done show rather clearly that whatever decrease there is to be will come shortly after the operation, and that the longer one waits, the less likelihood there will be of finding a lowered excretion. In other words, it seems that the function will have returned to normal, or practically normal, within from twenty-four to forty-eight hours. To recapitulate briefly, when the test was done within six hours after the operation, the average decrease varied between 19.4 per cent. and 25.1 per cent. Compare this with those cases in which the tests were performed between twenty-four and forty-eight hours after operation, in which the average decrease is found to be only 2.2 per cent. It is fair to assume that of the cases of this last group numerous ones showed a considerable decrease of function within the first few hours, but that it had returned to normal in the twenty-four or more hours before the test was done.

Following are a few cases illustrating this:

CASE 1.—Man, aged 40 (case quoted above also).

Test: February 19, 1 c.c. phthalein; voided in two hours. Phthalein, 54.3 per cent.

Operation: February 25, spinal anesthesia, plus ether. Carcinoma of rectum.

Test: February 25, patient unconscious and in shock; 1 c.c. phthalein, three hours after operation; catheterized. Phthalein excretion, 00.0 per cent.

Test: February 26—day after operation—patient better; 1 c.c. phthalein; excretion, 50.0 per cent.

This case shows total inhibition of phenolsulphonephthalein excretion up to five hours after operation, but return to nearly normal the next day.

CASE 2.—Man, aged 49; well nourished.

Test: November 2, 1 c.c. phthalein; voided. Excretion, 56.8 per cent.

Operation: November 3, 1 c.c. phthalein, three hours and seven minutes after operation; catheterized. Excretion, 39.3 per cent.

Test: Day after operation, 1 c.c. phthalein, voided. Excretion, 57.0 per cent.

CASE 3.—Man, aged 19. Well nourished. Hernia.

Test: November 7, 1 c.c. phthalein. Excretion, 69.4 per cent.

Operation: November 10, hernia.

Test: 1 c.c. phthalein while patient still unconscious; excretion, 00.0 per cent.

Test: November 11—day after operation—1 c.c. phthalein. Catheterized. Excretion, 57.0 per cent.

This is a return to nearly normal in twenty-four hours after a drop to zero.

CASE 4.—Man, aged 37, well nourished. Cholecystitis.

Test: October 8, 1 c.c. phthalein; voided in two hours. Excretion, 66.6 per cent.

Operation: October 9, cholecystectomy.

Test: October 9, 1 c.c. phthalein, six hours and thirty-five minutes after operation. Excretion, 40.3 per cent.

Test: October 10, day after operation, 1 c.c. phthalein; voided. Excretion, 80.5 per cent.

In this case the output has not only returned to normal, but has even increased by 13.9 per cent. on the day following operation.

The following case is interesting, as it was one of spinal anesthesia:

CASE 5.—Man, aged 69; well nourished. Op. litholapaxy.

	App. Time	One Hour Excretion
Day before operation.....	12 minutes	32.0 per cent.
Four hours after operation.....	16 minutes	22.7 per cent.
Twenty-eight hours after operation	8 minutes	44.4 per cent.

This again shows a rebound to a figure higher than the preoperative one.

#### THE EFFECT OF LAPAROTOMIES

The following seventy-five cases are laparotomies which were in the series, not including inguinal and femoral hernias. Ventral hernias in scars and umbilical hernias, however, are included, as they can fairly be called laparotomies. In each case the second test was done within six hours of the end of the operation. This group includes widely differing procedures, from simple exploration or rapid appendectomy to extensive intestinal resections or radical stomach surgery.

Number of cases, 75.

Average output before operation, 59.1 per cent.

Average output after operation, 47.2 per cent.

Difference ..... 11.9 per cent.

Decrease in output, 20.1 per cent.

This is, as might be expected, slightly higher than the general average decrease after ether.



## THE EFFECT OF OPERATION ON CANCER CASES

It was thought worth while to analyze this group, which includes all the cases of operation for malignant disease—mostly carcinoma, but with a few cases of sarcoma. The operations were of all sorts.

Number of cases, 24.

Output before operation, 54.1 per cent.

Output after operation, 37.7 per cent.

Difference ..... 16.4 per cent.

Decrease in output, 30.3 per cent.

These figures seem to show two things: first, that in accordance with the patient's more or less reduced condition which results from harboring such a growth, the output before operation is lower than normal; and second, that for the same reason the kidneys show the effect of the ether and operation more than the average.

From our series of cases it would be possible to pick out many isolated ones, each showing some point or other of interest, but that would entail the use of a great deal of space and would not prove anything definitely, so that it does not seem advisable to do so at this time.

## CONCLUSIONS

In drawing these conclusions we would state that by the term "renal function" is meant "renal function as shown by the phenolsulphonephthalein test." Also, that it does not seem possible to draw a sharp line between the effect of the anesthetic, and the effect of the operation *per se*, and this must be borne in mind in interpreting the results.

1. The output of phenolsulphonephthalein by the kidneys grows progressively less with advancing years.

2. There is a normal daily variation in phenolsulphonephthalein excretion, influenced by many factors, the normal limits of which cannot be defined.

3. After operations under ether there is a decreased output of phenolsulphonephthalein, this decrease being greater in laparotomies than in the general average, and considerably greater in cancer cases.

4. As a general proposition, the sooner after operation the test is done the greater will be the decrease, and the output will have returned to about normal in from twenty-four to forty-eight hours.

5. The more ether that is used, and the longer the operation, the greater will be the decrease in phenolsulphonephthalein excretion.

6. Certain cases will not show decrease, but either no change or increase. Just which cases do, or will do this, cannot be stated.

7. Certain cases will show great decrease or almost total inhibition of the excretion without discoverable cause. Personal idiosyncrasy may enter into this.

8. Shock will cause great decrease in phenolsulphonephthalein excretion. So also will any condition of much impaired vitality.

9. There is no definite relation between decreased drug excretion and the occurrence of albuminuria after operation.

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# INTESTINAL OBSTRUCTION

AN EXPERIMENTAL STUDY OF THE CAUSES OF SYMPTOMS  
AND DEATH \*

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This experimental study was undertaken for the purpose of explaining certain apparent contradictions in the deductions drawn from experimental work on the development of symptoms and the cause of death in intestinal obstruction. Although a toxin has not been demonstrated in the blood, most observers believe that symptoms and death are the result of a toxemia. The source of the toxin and its physical and chemical properties have not been agreed on, and the manner by which the toxin is taken into the body has not been made clear.

Without attempting an extensive review of the literature, the views held by certain recent workers will be briefly stated.

Murphy and Vincent<sup>1</sup> (1911) from experiments on cats, believe that symptoms and death in intestinal obstruction were the result of the elaboration and absorption of a toxic substance from the obstructed intestine. The toxic substance was believed to be a non-soluble substance which was destroyed by boiling. They emphasized circulatory disturbance, especially venous obstruction, as a factor in causing acute and early symptoms. The toxicity of the loop content was tested with intestine obstructed for from four to six hours. They further believed that the toxin was the result of bacterial growth.

Hartwell and Hogue<sup>2</sup> (1912) from experimental study on dogs, concluded that death in intestinal obstruction was due to the absorption of a toxic substance as a result of damage done to the intestinal mucosa. They draw no conclusions as to the source of the toxic sub-

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1. Murphy and Vincent: Boston Med. and Surg. Jour., 1911, clxv, 684.

2. Hartwell, John A., and Hogue, J. P.: Am. Jour. Med. Sc., 1912, cxliii, 357; Experimental Obstruction in Dogs with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution. The Journal A. M. A., July 13, 1912, p. 82; Jour. Exper. Med., 1913, xviii, 139. Hartwell, John A., Hogue, J. P., and Beckman, Fenwick: An Experimental Study of Intestinal Obstruction, THE ARCHIVES INT. MED., May 15, 1914, p. 701.

stance. It is stated that it may be normally present or may result from stagnation. The severity of the symptoms they believe to be in direct ratio to the extent of the damage to the intestinal mucosa. The loss of body fluids is emphasized as a factor in the causation of death. The toxicity of the content of the obstructed bowel was not studied.

Whipple, Stone and Bernheim,<sup>3</sup> and Davis<sup>4</sup> (1912, 1913, 1914) publish the result of experiments on dogs with intestinal obstruction. They believed that death after intestinal obstruction is due to the absorption of a toxin secreted by the intestinal mucosa, and that this toxic secretion can be derived from the bowel wall without a demonstrable change being present in the intestinal mucosa. The perverted secretion is held to be specific for the duodenum and high jejunum, and the toxin to be a soluble substance which is not destroyed by autolysis or boiling in non-coagulable fluid. The toxic material studied was obtained from simple obstruction of isolated duodenojejunal loops of from thirty-six to seventy-two hours' duration. A characteristic symptomatology and pathologic change following the injection of the toxic intestinal content were described.

To summarize: all these observers believe that death is due to a toxemia. Opinions are in conflict as to the solubility of the toxin and its filterability; also as regards the origin of the toxic substance. In a toxemia, two factors must be present, the production of the toxin and the absorption of the toxin. The severity of the toxemia, that is, the symptoms depend on both factors. In the experimental work referred to, these two factors have not been clearly distinguished. The differences in opinion are not so striking when they are analyzed. For example, the opinion of Hartwell and Hoguet in maintaining that the severity of the symptoms depends on the extent of the damage to the intestinal mucosa is not necessarily opposed to that of Whipple and his co-workers in their statement that the toxin may be developed without great changes in the mucosa, for the reason that damage to the mucosa is essential to the absorption of the toxin as is proven by the fact that the toxin is not absorbed from the normal mucosa. Also the terms "damaged mucosa" and "perverted secretion" may not represent different processes. The chemical and physical characteristics of the toxic material were studied by such different methods that varying statements in regard to these properties are not surprising. Murphy and Vincent worked with the content of a strangulated obstruction of from four to six hours' duration. Whipple, Stone, and

3. Whipple, Stone and Bernheim: *Bull. Johns Hopkins Hosp.*, 1912, xxiii, 159; *Jour. Exper. Med.*, 1913, xvii, 286; *Jour. Exper. Med.*, 1913, xvii, 307; *Ann. Surg.*, 1914, lix, 714.

4. Davis, D. M.: *Bull. Johns Hopkins Hosp.*, 1914, xxv, 33.

Bernheim worked with the content of isolated intestinal loops obstructed for from forty-eight to seventy-two hours without strangulation. That the toxicity and the characteristics of the intestinal content should differ after a longer or shorter period of obstruction is not surprising. Thus, when the problem of intestinal obstruction is reduced to its fundamentals, it seems that there is not such a wide difference between the opinions of the experimental workers, except as to source and the physical and chemical characteristics of the toxic material which is responsible for the symptoms and death, the apparently contradictory statements being more the result of undue emphasis on different factors, and the failure to distinguish clearly between the production and the absorption of the toxin.

In this experimental study we have attempted to determine a proper relationship of the various factors and to reconcile, so far as possible, the differences in opinion, and to determine more definitely the factors which lead to the production of this toxic substance. The experiments were carried out on dogs; the operations were done under complete anesthesia with a careful aseptic technic. All animals which did not die from the toxemia were sacrificed by the administration of chloroform. Only one experiment of each subdivision is described in detail. A sufficient number of observations were made in each instance to satisfy us of the correctness of the conclusion, eighty-eight experiments being performed in this study.

#### GROUP I.—CLOSED DUODENAL OR HIGH JEJUNAL LOOPS

To show certain characteristics of the intestinal contents after simple obstruction for from seventy-two to one hundred and two hours, and to define the pathologic changes and symptoms following the injection of this intestinal content into another animal.

EXPERIMENT 35.—Dog. Weight, 8,400 gm. Laparotomy. Heavy tapes tied tightly around duodenum just distal to the pancreatic duct and around the jejunum about 30 or 40 cm. distalward. Gastro-enterostomy just distal to tape around jejunum.

Twenty-four hours: Animal is up. Has not vomited.

Forty-eight hours: Animal lies coiled up in cage. No vomiting.

Seventy-two hours: Animal found dead. Weight after death, 8,000 gm.

*Necropsy.*—The abdominal cavity shows nothing abnormal except the obstructed loop. The remainder of the intestine is not distended. Content of the loop is a thick, paste-like fluid, slightly blood-tinged, and having a foul odor. Microscopic examination of the bowel wall shows a complete loss of mucosa except for a few of the deeper tubules.

EXPERIMENT 48.—(a) Dog. Weight, 1,100 gm. Laparotomy. Jejunum sectioned twice at 10 cm. and 50 cm. distal to duodenojejunal junction. The four ends turned in. Intestinal continuity reestablished by lateral anastomosis between distal and proximal stump. Abdomen closed. The operation gave an isolated obstructed loop of jejunum.



Twenty-four hours: Animal is up. Does not look sick.  
Forty-eight hours: Animal is drowsy. Lies coiled up in cage.  
Seventy-two hours: Dog found dead.

*Necropsy*.—Nothing abnormal found except in abdominal cavity. The peritoneum is injected. There is some free fluid. The entire small intestine is distended, the jejunum more than the ileum. The mucosa of the duodenum and jejunum is swollen and red. The isolated loop is tremendously distended and is discolored. There are several areas which are very thin and one pinpoint perforation through which the loop content is escaping. The contents remaining consist of 75 c.c. of a thick, brown fluid of foul odor.

(b) Of the fluid obtained from the loop, 15 c.c. was diluted to 30 c.c. with distilled water, and injected into the peritoneal cavity of a dog weighing 4,400 gm. at 11 a. m.

12 m.: Animal is vomiting.

1 p. m.: Dog looks very sick. Vomiting and fluid stools.

2 p. m.: Animal moribund.

3:30 p. m.: Dead.

*Necropsy*.—The peritoneum is intensely injected. The mucosa of the stomach looks normal. The mucosa of the duodenum beginning sharply about 0.5 cm. from the pylorus is swollen and has a deep red color. The jejunum shows a similar condition. The mucosa of the ileum and large intestine shows a less marked injection. Over the swollen, reddened mucosa of the duodenum and jejunum there is a thick, white exudate which can be lifted off in flakes.

(c) Another portion of 15 c.c. of obstructed loop content was diluted to 30 c.c. with distilled water. The container was placed in boiling water for ten minutes, the fluid being actively stirred. There was a heavy granular coagulum formed. The fluid was then boiled vigorously over a free flame for one minute. The supernatant fluid and the coagulum were injected into the peritoneal cavity of a dog weighing 4,700 gm. at 10:30 a. m.

12 m.: Dog is up.

1 p. m.: Animal looks very sick. Has not vomited.

3 p. m.: Animal dead.

*Necropsy*.—On opening the abdomen, there is a small amount of colorless free fluid. Peritoneum slightly injected. The coagulum of injected fluid lies in the omentum. The intestine is not noticeably distended. The mucosa of the stomach is normal. The mucosa of the duodenum and jejunum is swollen and red. The mucosa of the ileum and colon is less injected. Culture made from the abdominal cavity gave no growth.

(d) Of the remaining loop content, 40 c.c. was diluted to 80 c.c. with distilled water. Centrifuged at high speed twenty-five minutes. The supernatant fluid was filtered through a coarse clay filter and the filtrate passed through a Berkefeld filter. A culture made from the filtrate showed no growth. Of this sterile filtrate, 30 c.c. (an amount which, taking into account the volume of the residue and the loss from evaporation, represented at least one-half of the material in solution in the diluted intestinal loop content) were given intravenously to a dog weighing 5,300 gm. at 9:45 a. m.

10:30 a. m.: The animal looks sick. Has vomited twice.

4 p. m.: The dog still looks drowsy. No more vomiting.

The following morning, the animal did not eat, but recovered during the day and showed no more symptoms.

(e) The residue from the centrifugation of 40 c.c. of the obstructed loop fluid (d) was made up to 80 c.c. with distilled water, placed in bottle containing several drops of toluol, and set aside at room temperature for forty days. At this time the fluid had separated into two distinct layers, a bottom layer of an opalescent fluid and a top layer of fat-like substance. The fluid at the bottom was filtered through a clay filter and the filtrate passed through a Berkefeld filter. Culture of the latter filtrate gave no growth. Thirty c.c. of the filtrate was given intravenously to a dog weighing 5,700 gm. at 9 a. m.

11 a. m.: Animal looks sick. Has vomited several times, and has passed two fluid stools.

1 p. m.: Dog looks very sick.

6 p. m.: Animal looks distinctly better.

The following morning the animal was sacrificed. Necropsy showed nothing noticeably abnormal.

EXPERIMENT 36.—(a) Dog. Weight, 7,350 gm. Laparotomy. Tape tied around duodenum just below opening of pancreatic duct. Another tape placed around upper jejunum. Gastro-enterostomy just distal to distal tape.

Twenty-four hours: Animal is up. Eats and drinks. Vomited once.

Fifty-four hours: Dog is up. Seems slightly drowsy. Anesthetized and abdomen opened. Peritoneal cavity looks normal. The loop of bowel between the tapes is slightly distended. Peristalsis normal. Abdomen closed.

Seventy-two hours: Dog is up. Eats and drinks.

One hundred and two hours: Dog is up. Responds to attention. Weight, 5,400 gm. Animal anesthetized. Abdomen opened. Peritoneal cavity normal. The obstructed duodenojejunal loop was excised. The duodenal and jejunal stumps turned in. The loop is moderately distended. Peristalsis present. The content of the loop measured 100 c.c. The fluid was a thick, paste-like material of foul odor. In gross the mucosa looked strikingly normal. On microscopic examination the mucosa was edematous, infiltrated with mononuclear and polymorphonuclear leukocytes. The epithelial cells in deeper layers of the mucosa showed very little change; from the tips of the villi they were swollen or completely lost.

(b) Of the fluid from the obstructed loop 5 c.c. were injected intravenously into a dog weighing 6,700 gm. at 10 a. m.

10:30 a. m.: Immediately after recovery from ether, the animal began to vomit and pass fluid stools.

12 m.: Animal moribund.

2 p. m.: Dog having convulsions.

2:30 p. m.: Dead.

*Necropsy.*—Immediate. Abdominal cavity contained no free fluid. Intestines seemed full but not distended. The entire small bowel had a bluish color. Peristalsis very marked and the contractions rapid. There were no normally progressing waves. On opening the gastro-intestinal tract, the stomach looked normal. Beginning sharply at the pylorus and extending through the jejunum, ileum, and colon, the mucosa was swollen and of a deep red color. The lumen was filled with blood-tinged mucus. The liver, spleen and kidneys were full of dark blood.

(c) The dog from which the obstructed loop was excised made an uneventful recovery and remained quite well for some weeks, when the animal died from perforation of the duodenal stump from a collection of meat bones.

These observations justify the following statements:

1. Dogs with isolated obstructed duodenojejunal loop die without infection of the general peritoneal cavity or any evidence that the cause of death is any other than factors immediately associated with the isolated obstructed loop. The symptoms which follow the operation are fairly constant. For the first twenty-four hours after operation, the condition of the animal is not different from that after any laparotomy. Usually at forty-eight hours, the animal appears drowsy and does not eat and vomits. The animal may rapidly become more apathetic and die in from seventy-two to ninety-six hours.

2. Excessive vomiting or extreme loss in body weight are not necessarily factors in the symptoms as is shown by Experiment 35.

3. That symptoms are not the result of the loss of function of the duodenum and upper jejunum as once held by Matthews, is proved by Experiment 36, in which the symptoms cleared up after total excision of this part of the intestine.

4. The content of the obstructed loop is a toxic fluid which, when introduced in comparatively small doses into the circulation of normal dogs, causes severe vomiting, fluid stools, and death. Associated with the symptoms, there is a characteristic pathologic picture which consists in an acute hemorrhagic enteritis, especially marked in the duodenum and jejunum.

5. The toxicity of the obstructed loop content is not destroyed by heating to 60 C. until sterile, or even by boiling.

6. The toxicity of the fluid is very much decreased by filtration through a Berkefeld filter, so that to produce death a dose of filtrate corresponding to several times the lethal dose of unfiltered fluid is necessary.

7. The amount of filterable toxin is increased by prolonged autolysis.

8. In no case did an animal show symptoms without demonstrable changes in the mucosa.

#### GROUP II.—CLOSED LOOPS OF ILEUM

To show that obstructed ileum may cause the same pathologic changes and symptoms as obstructed duodenum or jejunum.

EXPERIMENT 41.—(a) Small dog. Laparotomy. Two tapes tied around the ileum at distances of about 10 cm. and 40 cm. from the ileocecal valve. The continuity of the intestinal lumen was reestablished by a lateral anastomosis between segments of the ileum proximal and distal to the closed loop.

Twenty-four hours: Dog is up. Eats sparingly.

Forty-eight hours: Animal is up. Has a diarrhea. Vomited several times during the day.

Seventy-two hours: Found dead.

*Necropsy.*—Abdominal cavity contained a small amount of free fluid. Peritoneal inflammatory signs limited to region of entero-enterostomy. The isolated loop is moderately distended. There is a perforation and the intestinal content is passing into the peritoneal cavity. The stomach is not distended, and the mucosa looks normal. The small bowel is somewhat distended, and the mucosa of the duodenum and jejunum is swollen and red. The lumen of the intestine is filled with a thick, soup-like fluid. Microscopic examination of the isolated loop shows extensive degeneration of the mucosa. Of the content of the loop, 5 c.c. of a thick, paste-like fluid of a foul odor was collected.

(b) Of the loop content, 2 c.c. was given intravenously to a dog weighing 4,100 gm. at 11 a. m.

1 p. m.: Animal is lying down. Respiration deep. Looks very sick. Has vomited several times.

2 p. m.: Animal completely prostrate. Has passed several fluid stools containing blood.

3 p. m.: Animal dead.

*Necropsy*.—Abdominal cavity contains no free fluid. Stomach normal. The mucosa of the duodenum and jejunum is swollen and deep red in color. The mucosa of the ileum shows a less marked change. The large bowel contains a large quantity of blood-stained mucus.

This experiment illustrates the fact that obstruction of an isolated loop of ileum may produce symptoms and death in seventy-two hours, and that the content of the obstructed loop is a toxic fluid which, when given intravenously, produces symptoms and pathologic changes identical with those obtained from injection of the contents of obstructed duodenojejunal loops. That isolated obstructed loops of ileum may, under certain conditions, be compatible with life, has been demonstrated by Halsted and will be referred to again in this paper. It is significant in this experiment that examination of the loop wall showed marked nutritional changes.

#### GROUP III.—ISOLATED, OBSTRUCTED LOOPS WITH INTERFERENCE TO THE BLOOD-SUPPLY

To show the effect of the circulatory disturbance on the development of symptoms and the formation of the toxin.

EXPERIMENT 80.—Dog. Weight, 6,060 gm. Laparotomy. A tape was tied around the jejunum just below the duodenojejunal junction. Another tape tied 30 cm. distalward. The veins in the mesentery of the segment of bowel between the tapes were ligated. The bowel became immediately swollen and blue. Abdomen closed.

Five hours: Animal vomiting.

Seven hours: Dog looks desperately sick. Vomiting.

Twenty-two hours: Found dead.

*Necropsy*.—Showed the obstructed segment soft, friable. Content of the loop which consisted in a thick, bloody fluid, was emptying into the peritoneal cavity through a perforation. Peritoneum showed very little change.

EXPERIMENT 40.—Small dog. Laparotomy. Thirty cm. of jejunum isolated. Ends turned in. The continuity of the intestinal lumen was reestablished by lateral anastomosis. The arteries in the mesentery of the isolated loop were ligated. The loop was completely wrapped up in omentum.

Seven hours: The animal lies coiled up in cage. Does not respond to attention. No vomiting.

Twenty-one hours: Dead.

*Necropsy*.—The abdominal cavity contains blood-stained fluid. The isolated loop is completely surrounded by omentum. The loop is completely gangrenous. It contains 20 c.c. of thick, blood-stained, paste-like material the usual odor.

EXPERIMENT 84.—Dog. Weight, 4,200 gm. Laparotomy. Four tapes were tied around the upper portion of the jejunum so as completely to occlude three segments of the bowel. The circulation in the proximal segment was not disturbed. The veins in the mesentery of the middle segment and the arteries in the mesentery of the distal segment were ligated. The segment with the

venous occlusion immediately became swollen and hemorrhagic. The segment with the arterial ligation became pale. Abdomen closed.

Two hours: Animal is vomiting repeatedly. Looks sick.

Seventeen hours: Dog found dead.

*Necropsy*.—The peritoneal cavity contains approximately 100 c.c. of a thin, blood-stained fluid. No evidence of peritonitis. The segment of bowel without circulatory disturbance appears normal except immediately adjacent to tapes. The lumen contains about 1 c.c. of a mucus-like fluid which is blood-stained in the region of the obstructing tapes. The segment with the venous occlusion is distended, swollen, and dark red in color. The content consists of 40 c.c. of a thick, foul-smelling fluid, the color of a potassium permanganate solution. The segment of bowel with the arterial ligation is distended and yellowish-brown in color. The walls are thin. The contents consist of 15 c.c. of a slightly blood-stained, mucus-like material. With contents of the loops, the following experiments were carried out.

(a) Of the contents of the segments with venous obstruction, 10 c.c. were given intravenously to a dog weighing 6,900 gm. at 10:45 a. m.

11:30 a. m.: Vomiting. Looks sick.

3:15 p. m.: Vomiting.

5 p. m.: The animal lies coiled up in cage. Does not respond to attention. Sacrificed. Necropsy showed the peritoneal cavity normal. The lumen of the intestine contains blood-stained mucus. There is a slight injection of the mucosa of the duodenum and jejunum.

(b) Of the contents of the segment with venous obstruction, 20 c.c. was diluted to 40 c.c. with distilled water. Centrifuged twenty minutes. The supernatant fluid was filtered through paper and the filtrate again filtered through a Berkefeld filter. Amount of filtrate obtained, 23 c.c. The entire filtrate was given intravenously to a dog weighing 4,850 gm. Following the injection, the animal recovered immediately and did not show any symptoms. Three hours after the injection the animal ate a heavy meal.

(c) Of the fluid from the segment with arterial obstruction, 6 c.c. was given intravenously to a dog weighing 5,700 gm. at 11 a. m.

11:30 a. m.: Vomited. Passed stool.

3 p. m.: Vomiting. Numerous fluid stools.

5 p. m.: Dog is moribund. Sacrificed. Necropsy showed the bowel full of blood-stained mucus. The mucosa of the duodenum and jejunum was swollen and dark red in color. The ileum showed less change.

(d) In this experiment, the fluid from the peritoneal cavity was not tested, but in other experiments it was found that the fluid accumulating in the peritoneal cavity after strangulation of loops of bowel may be sterile at death, and such fluid may be given intravenously in large doses without producing symptoms.

Three experiments prove the following statements:

1. Animals with obstructed segment of bowel in which there is a disturbance in the blood-supply develop symptoms more rapidly and die in much shorter time than animals with obstructed segments of bowel in which there is no nutritional disturbance.

2. The fluid accumulating in segments of bowel with vascular disturbance, especially arterial obstructions, is very toxic in a period of less than twenty-four hours, at which time an obstructed segment of bowel without vascular disturbance contains practically no content.

3. The Berkefeld filtrate from the contents of an obstructed segment of bowel with venous obstruction of twenty-four hours or less



duration, may be injected intravenously in healthy dogs in comparatively large dose, without causing symptoms.

#### GROUP IV.—ISOLATED, DRAINED INTESTINAL LOOPS

To contrast the amount of secretion from the jejunum with that from the ileum, and to show the influence of the difference in the amount of secretion in the production of symptoms.

EXPERIMENT 10.—Dec. 18, 1912: Dog. Laparotomy. The jejunum was sectioned about 10 cm. distal to duodenojejunal junction and again 30 cm. more distalward. The ends of the proximal and distal stumps inverted and the continuity of the intestinal lumen reestablished by lateral entero-enterostomy. The distal end of the isolated segment was inverted and the proximal end pulled out through a stab wound in the flank. Abdomen closed.

Jan. 15, 1913: The animal made a good recovery, and is in good condition. The isolated loop is draining a clear fluid.

Feb. 5, 1913: The animal is in good condition. At 1 p. m. under ether anesthesia the drained end was inverted and the skin closed over.

Feb. 6, 1913: Dog in good condition. Has shown no symptoms.

Feb. 7, 1913: Animal vomited once.

Feb. 8, 1913: Animal is up. Does not eat. Pulse 200. Animal looks sick. At 1 p. m. the incision was opened and the inverted distal end was opened. The isolated loop contained 100 c.c. of a thick, paste-like material having the typical foul odor of the obstructed loops.

March 15, 1913: Following the drainage of the isolated loop, the animal recovered in three or four days to normal condition, and remained in good condition until to-day, when it was noted that the dog was somewhat drowsy and did not eat. The enterostomy has contracted to a small opening 1 mm. in diameter, through which is discharging a small amount of a thick, paste-like material. Under ether anesthesia, the end of the isolated segment of bowel was pulled out so that the drainage opening was much larger.

May 22, 1913: Following the operation, the animal again became quite normal and healthy. The isolated loop is draining a thin, colorless fluid. To-day the drained end of the isolated loop was again closed by inversion.

May 23, 1913: Animal is up. Does not eat. Vomited once.

May 24, 1913: Dog looks sick. Vomited several times during day.

May 25, 1913: Animal still vomiting.

May 26, 1913: No vomiting. Drowsy. Temperature 102. Pulse 160.

May 27, 1913: Animal in same condition. Laparotomy. Peritoneal cavity normal, except for the isolated segment of bowel which is tremendously distended with a yellowish white fluid. The end of the loop was brought out through a stab wound and left open.

May 28, 1913: Animal found dead. Necropsy showed the isolated loop quite empty. There were areas of hemorrhage and congestion; otherwise abdominal contents normal.

Of the fluid obtained from the loop, a culture showed abundant bacterial growth. Fifteen c.c. of the fluid were given intravenously to a dog weighing 5,200 gm. The animal remained limp and died four hours later. Necropsy showed the abdominal organs tremendously congested. The mucosa of the duodenum and jejunum was swollen and red.

EXPERIMENT 43.—Dec. 5, 1913: Strong dog. Laparotomy. About 20 cm. of the lower end of the ileum was isolated. The intestinal continuity was reestablished by end to end suture. The distal end of the isolated loop was inverted and the proximal end drawn through a stab wound in the flank.

Dec. 23, 1913: Following operation, the animal had a profuse diarrhea which has now ceased. Eats well. Is gaining weight. The enterostomy has contracted until it admits only a small probe.



Dec. 31, 1913: Animal in excellent condition. The enterostomy has closed except for a small pin-point opening through which there is no visible discharge. Pressure on the surrounding tissue, however, caused a small drop of fluid to exude.

Jan. 17, 1914: The dog is in excellent health. No visible drainage from isolated loop. An incision was made by the side of the sinus which seemed to communicate with the lumen of the isolated loop and a tape tied tightly around the bowel. Skin closed over tape.

Jan. 21, 1914: Animal has remained in perfect health. No symptoms. The abdomen was opened and the isolated loop inspected. It has the appearance of quite normal bowel. Peristalsis present. Loop apparently empty. Abdomen closed. Subcutaneous tape which remained tightly tied around the bowel removed.

March 15, 1914: Enterostomy completely closed. Animal healthy.

April 16, 1914: The dog is in perfect health. Very fat. Weight, 16 kg. The enterostomy remains completely closed. Skin over site of drainage perfectly smooth. Laparotomy. The isolated loop was delivered. It was slightly distended, especially at its distal (inverted) end. Peristalsis active. Careful examination showed that the loop was quite isolated and completely closed at both ends. The distal end of the loop was excised and the content removed. The content collected consisted of 35 gm. of a thick, white, paste-like material. The distal end of the loop was inverted. Abdomen closed. A culture from the content of the closed loop gave abundant growth of bacilli and cocci. Microscopic examination showed the material to consist of bacteria, exfoliated epithelial cells, and a granular detritus.

Of the content of the closed loop, 2 gm. were diluted to 10 c.c. with distilled water and injected intravenously into a dog weighing 4,600 gm. at 10 a. m.

10:15 a. m.: Animal prostrate.

11 a. m.: Looks desperately sick. No vomiting. Passed semisolid stool.

12 m.: Animal lies with muscles rigid. Blood-stained mucus passed per rectum.

12:30 p. m.: Dead.

*Necropsy.*—Peritoneum normal. Liver, kidneys, and spleen congested. Entire small bowel has a bluish color. Mucosa of stomach normal. Beginning sharply at the pylorus, the mucosa of the duodenum is swollen and is a dark red color. The mucosa is covered by a layer of mucus. The jejunum shows a similar condition. The injection of the mucosa of the ileum and colon is less marked.

Original animal died third day after turning in loop end.

These experiments illustrate that isolated, drained segments of jejunum differ from isolated, drained segments of ileum in the following manner:

1. Isolated, drained loops of jejunum discharge constantly a relatively large quantity of a thin fluid, while isolated, drained loops of ileum discharge very little.

2. Following the closure of such jejunal loops, the animal develops in the course of from seventy-two to ninety-six hours, symptoms of grave intoxication associated with marked distention of the occluded loop and an accumulation of a toxic content. The enterostomy of an isolated, drained loop of ileum may close and the loop may be completely occluded for long periods of time without signs of intoxication. Such a closure is associated with very little and a gradual distention

of the bowel. The content of such a loop may be very toxic without the animal showing any signs of intoxication. Any operative procedure leading to damage of the mucosa results in symptoms.

#### GROUP V.—THORACIC DUCT EXPERIMENTS

To prove that the symptoms are due to a toxemia and to illustrate the effect of strangulation or distention of the intestine on the absorption of the toxin.

EXPERIMENT 38.—Large, strong dog. Cannula inserted into the thoracic duct at 10 a. m. Fluid from duct collected in sterile tubes.

11:10 a. m.: Laparotomy. Two tapes tied around the jejunum so as to include about 40 cm. of intestine. All of the veins in the mesentery of the occluded loop ligated. Abdomen closed.

11:20 a. m.: Four minutes after ligation of first vein of mesentery, there was sudden change in the thoracic duct fluid. It became blood-tinged and on microscopic examination, showed numerous red blood-cells.

1:30 p. m.: Animal still alive. Fluid from the thoracic duct is dark-red color. Flowing slowly. Coagulates easily.

3:30 p. m.: Animal died.

*Necropsy.*—Chest normal. Abdomen contains 50 c.c. blood-stained fluid. Culture taken. Fluid saved. The obstructed loop is distended, tense, and filled with a thick, bloody fluid. The remainder of the intestine is contracted. The mucosa of the jejunum and duodenum above the proximal tape is injected and contains a thick, mucus-like fluid which was saved. The mesentery of the obstructed jejunal segment is thickened and hemorrhagic. The lymph-glands at the root of the mesentery are swollen, edematous, and blood-stained.

The fluid from the thoracic duct before ligation of the mesenteric veins, measured 125 c.c.; after obstruction, 150 c.c. Cultures taken from thoracic duct fluid, taken every hour during experiment, showed no growth. Also cultures from the mesenteric lymph glands were negative.

Two medium-sized dogs were not given food for twelve hours, and were used for the following experiments:

(a) The fluid from the coagulated thoracic duct before the obstruction of the bowel (kept on ice over night) was pressed out and injected into jugular vein. The animal vomited once five minutes after injection, but showed no more symptoms.

(b) The fluid from the thoracic duct after obstruction was gotten in a similar manner and injected into the jugular vein. The animal showed no symptoms.

(c) Twenty c.c. of the peritoneal fluid given intravenously. Animal showed no symptoms.

(d) Ten c.c. of the content of the segment of bowel above the proximal tape, diluted to 50 c.c. with distilled water, filtered through two layers of gauze. Filtrate (40 c.c.) injected intravenously. During the injection, animal became quite limp. One-half hour later animal had completely recovered and showed no more symptoms.

(e) Ten c.c. of the content of the obstructed loop, diluted to 20 c.c. with distilled water, filtered through gauze, injected intravenously. The animal looked sick, and would not eat for twenty-four hours, but did not vomit or pass fluid stools. Complete recovery.

EXPERIMENT 37.—Dog. Weight, 10,800 gm. Laparotomy. Tape tied around duodenum just distal to the opening of pancreatic duct. Another tape tied around jejunum 40 cm. distal to duodenojejunal junction. Gastrojejunostomy distal to distal loop. Abdomen closed. Animal ran the usual course. At the end of ninety-six hours, animal was very toxic. Sacrificed. Occluded loop

was distended and contained 100 c.c. of a thick, paste-like material which was collected and used in the following experiment.

A cannula was inserted in the thoracic duct of a strong dog. The fluid collected in sterile tubes. The abdomen was opened and a segment of jejunum was obstructed between tapes. The content of the ninety-six-hour obstructed loop was injected into the occluded loop, and the veins of the mesentery to the obstructed segment ligated. Following the ligation of the veins, the fluid from the thoracic duct became blood-stained. The fluid was collected for four and one-half hours, at which time the animal died. Amount obtained, 75 c.c.

The fluid was kept on ice over night, the fibrin was separated by squeezing through gauze. The entire filtrate was injected under local anesthesia into the jugular vein of a small dog at 9:30 a. m.

10 a. m.: Animal vomiting.

10:15 a. m.: Passed fluid stool.

12 m.: Animal looks desperately sick.

1 p. m.: Dead.

*Necropsy.*—Chest contains a small amount of free fluid. Lungs are edematous. No evidence of thrombosis or embolism. Peritoneal cavity normal. Intestine markedly contracted in rings. Kidneys, liver and spleen congested. Stomach normal. Mucosa of duodenum and jejunum swollen and red. Mucosa of rectum and colon also injected. Ileum normal.

EXPERIMENT 34.—Dog. Weight, 5,000 gm. Laparotomy. Tapes tied around upper jejunum, from 50 to 60 cm. apart. Gastro-enterostomy distal to distal tape. The animal developed the usual symptoms. Found dead after seventy-two hours. The content of the occluded loop was collected and used in the following experiment:

Medium-sized dog. Cannula inserted in thoracic duct. Laparotomy. Tape tied around jejunum. The bowel was sectioned 40 cm. distal to tape and a large cannula tied in proximal end. Following the section of the bowel, the thoracic duct fluid became bloody, but in a few minutes became colorless again. The content of seventy-two-hour obstructed loop was injected into the isolated segment of jejunum. The cannula in the end of the bowel was then connected with water-bottle elevated four feet above the level of the abdomen. This caused a marked distention of the isolated loop of jejunum and immediately following the distention, the thoracic duct fluid became blood-stained. The loop was kept distended and the fluid collected for six hours, at which time the animal died. The fluid from the thoracic duct became more blood-stained as the experiment progressed. Also five hours after beginning of distention, the content of the distended loop was blood-stained. At death, the distended loop was bluish red in color and quite flabby. Microscopic section showed almost complete destruction of the mucosa.

The fluid which was collected from the thoracic duct, measured 75 c.c. Defibrinated and injected intravenously into dog weighing 3,800 gm. at 9 a. m. Animal recovered from anesthetic immediately.

10:30 a. m.: Passed formed stool.

11 a. m.: Vomited large amount of food material.

12 m.: Animal looks sick, shivering. No more vomiting.

The animal recovered during the afternoon and seemed quite well next morning.

These experiments illustrate the following points:

1. Following occlusion of the veins to a segment of bowel, there is immediately hemorrhage into the lymphatics. There is also very quickly an extensive destruction of the mucosa and hemorrhage into the lumen of the bowel.

2. Similar changes follow rapid distention of the bowel from increased pressure within the lumen.

3. With the introduction of the toxic contents of an obstructed, intestinal loop into the lumen of the bowel and the occlusion of the veins of loop containing the toxic fluid (Experiment 37), the fluid from the thoracic duct contains a toxic substance, which, when given to a normal dog, results in symptoms similar to those following the injection of the toxic loop content. The fact that such symptoms did not follow the injection of the fluid obtained from the thoracic duct after simple obstruction and ligation of mesenteric veins of a segment of normal bowel (Experiment 38), is probably a matter of dosage, for in the strangulated loops of six hours, the concentration of the toxin of the loop content is not great (Experiment 84). Another factor is also to be considered. From the fact that following acute venous stasis there is hemorrhage into lumen of the bowel and into the lymphatics suggests that there is free communication between the bowel lumen and the lymph-vascular system, but that this communication is not as free as it seems is shown by the fact that bacteria do not pass into the circulation as evidenced by contents from the thoracic duct remaining sterile. This suggests that the toxin only passes into the circulation in a soluble form, and the content of a strangulated loop for a period of six hours contains very little toxic substance which will pass through a filter. In the case in which the thoracic duct fluid was collected after strangulation of bowel containing toxic fluid, the content was that obtained after ninety-six hours of simple obstruction, at which time there is more soluble toxic material.

That the symptoms were not so severe following the injection of the thoracic duct fluid in Experiment 34 is also probably explained by dosage, for in this case the circulatory disturbance was not so rapid and the mucous membrane probably remained as a protective filter longer, as evidenced by the fact that the content of the distended loop was not noticeably blood-stained until five hours after the distention.

#### GROUP VI.—GALL-BLADDER OBSTRUCTION

To show that this toxin found in the content of obstructed, intestinal loops is not specifically a product of intestinal obstruction, and to show the influence of bacterial action on the production of this toxin in the gall-bladder.

The gall-bladder is a hollow viscus, lined with secreting epithelial cells, and embryologically derived from the primitive intestine. Under normal conditions, it contains no bacteria, and it seemed possible that experimental obstruction of the gall-bladder with and without the presence of bacteria might throw some light on the relation of the bacteria to the production of the toxin in intestinal obstruction.

EXPERIMENT 72.—(a) March 14, 1914: Dog. Weight, 10,600 gm. High right rectus incision. Gall-bladder emptied of bile. The cystic duct with cystic vessels ligated. Ten c.c. of blood was aspirated from a small mesenteric vein and injected into the gall-bladder. The gall-bladder was then partially separated from the liver, so as to further interfere with its blood-supply. Abdomen closed.

March 15, 1914: Animal is up. Looks well. No vomiting.

March 16, 1914: Dog eats. Does not seem abnormal. Sacrificed.

*Necropsy*.—Immediate. In the region of the gall-bladder there is a localized collection of blood-stained fluid. The gall-bladder looks gangrenous but has not ruptured. Excised *en bloc*. The contents consist of 6 c.c. of a thick, paste-like fluid. A culture taken gave no growth. Microscopic examination of the gall-bladder showed almost complete necrosis.

(b) The entire contents of the gall-bladder immediately after removal were injected intravenously into a dog weighing 10,400 gm. at 10:45 a. m.

11:15 a. m.: The animal is still drunk from ether. No vomiting.

12 m.: Dog seems perfectly normal.

5 p. m.: Has shown no symptoms. No vomiting. No fluid stools. The animal was quite well the following day.

EXPERIMENT 71.—(a) March 11, 1914: Dog. Weight, 13.5 kg. Laparotomy. Gall-bladder emptied of bile. Cystic duct and vessels ligated. With a syringe, 1 c.c. of duodenal contents aspirated. The material from the duodenum was mixed with 10 c.c. of blood aspirated from a mesenteric vein and injected into the gall-bladder. Abdomen closed.

March 12, 1914: Animal is vomiting. Looks sick.

March 13, 1914: Dog found dead.

*Necropsy*.—No free fluid in the peritoneal cavity. In the region of the gall-bladder there is a small amount of fluid. The gall-bladder is bluish red in color. Very little distended. The content consists of 2 c.c. of a thick, paste-like material. Microscopic examination of the gall-bladder shows almost complete necrosis. The mucosa of the duodenum and jejunum is swollen and red. There is a large quantity of mucus in the intestinal lumen.

(b) The entire content of the gall-bladder was given intravenously to a dog weighing 5 kg. at 10 a. m.

10:15 a. m.: Animal is up.

10:30 a. m.: Vomiting. Passing fluid stools.

3:30 p. m.: Animal is having muscle spasm.

5:30 p. m.: Animal is moribund. Sacrificed.

*Necropsy*.—Abdomen contains no free fluid. Spleen, liver and kidneys congested. The mucosa of the duodenum and jejunum is swollen and red. There is a large quantity of frothy blood-stained mucus in the intestinal lumen.

EXPERIMENT 73.—(a) March 17, 1914. Dog. Weight, 10 kg. Laparotomy. Gall-bladder emptied of bile. Jejunum aspirated. One drop of jejunal fluid mixed with 10 c.c. of sterile water and injected into gall-bladder. Abdomen closed.

March 18, 1914: Dog has vomited several times.

March 19, 1914: Animal does not eat. Anesthetized with very little ether. Abdominal wound opened. Gall-bladder distended. Dark blue in color. Excised *en bloc*. The content consists of 5 c.c. of a blood-stained fluid having the characteristic odor of obstructed intestinal contents. Abdomen closed. Microscopic examinations of the gall-bladder showed necrosis and infiltration with leukocytes.

(b) The entire content of the gall-bladder was made up to 10 c.c. with distilled water. Placed in a thermostat at 60 C. for twenty-four hours. Culture taken gave no growth. The fluid was given intravenously to a dog weighing 6.5 kg. at 10:30 a. m.

11:30 a. m.: Animal is up. Has shown no symptoms.



1 p. m.: Dog is lying down. Looks drowsy. Constantly protruding tongue as if nauseated.

2:30 p. m.: Animal has vomited twice. Looks sick.

3:30 p. m.: Animal still nauseated. Passed one semi-solid stool.

The dog recovered without further symptoms, and seemed quite well the following day. These experiments show:

1. The sterile gall-bladder of the dog can be obstructed and the blood-supply interfered with to the point of complete gangrene without the animal showing noticeable symptoms, and the fluid accumulating in such an obstructed gall-bladder can be given intravenously to healthy dogs without inducing symptoms.

2. Following the obstruction and interference of nutrition of the gall-bladder containing the bacteria of the intestine, the animal shows symptoms identical with those of intestinal obstruction, and the fluid accumulating in the gall-bladder when administered intravenously, even after sterilization of 60 C., produces symptoms and a pathologic picture identical with that following the injection of the content of an obstructed segment of intestine.

#### GROUP VII.—EXPERIMENTS ON A DOG IN WHICH A DRAINED JEJUNAL LOOP BECAME STERILE

To show the effect of bacteria on the production of the toxin in obstructed intestine and to show that the normal secretions of a draining loop of intestine are not toxic.

Jan. 23, 1913: Strong dog. Laparotomy. Jejunum sectioned near duodenojejunal junction and again 30 cm. below. The continuity of the intestinal lumen reestablished by end to end suture. The distal end of the isolated segment was inverted. The proximal end drawn through a stab wound in the flank and stitched to the peritoneum. Abdomen closed.

Feb. 15, 1913: Animal made an unusually good recovery, and is now healthy. The opening of the isolated segment of jejunum is open and there is a constant discharge of a thin, colorless fluid. A mushroom catheter was introduced into the isolated segment. The loop seemed quite empty. By pushing the catheter in and out, there was a marked increase in the peristalsis and the rate of secretion. The peristalsis waves drew the catheter inward.

Six c.c. of the secretion was collected and injected into the peritoneal cavity of a guinea-pig. The pig showed no symptoms.

Feb. 24, 1913: Animal healthy. Drained loop in same condition. By means of a catheter, 20 c.c. of the loop secretion was collected. Incubated at 37 C. for seventy-two hours. Of the incubated fluid, 5 c.c. injected into peritoneal cavity of a guinea-pig. Guinea-pig dead in twenty-four hours.

The remaining 15 c.c. of fluid heated in thermostat twenty-four hours at 70 C. Incubated twelve hours at 37 C. Heated again twenty-four hours at 65 C. Of this fluid, 5 c.c. were given intraperitoneally to a guinea-pig. Pig dead in twenty-two hours. Culture of fluid injected gave no growth. Culture from peritoneal cavity of pig after death gave a growth.

Oct. 15, 1913: Animal is in excellent health. Enterostomy is open and is constantly draining a thin colorless fluid. Peristalsis active and waves in normal direction. A culture made from some content aspirated from the isolated, drained loop remained sterile.

Oct. 20, 1913: Thirty c.c. of the isolated loop secretion was given intravenously to a small dog. The animal showed no symptoms.



Dec. 4, 1913: Three more cultures made at intervals from the secretion of the isolated jejunal loop have remained sterile. The animal is in excellent condition. Anesthetized. Laparotomy. The isolated loop was delivered and obstructed by a clamp made from two short glass rods covered with rubber tubing. An attempt was made to tie the clamp just tight enough to obstruct the lumen without causing necrosis. Abdomen closed.

Dec. 5, 1913: Animal is up. Eats. Seems quite well.

Dec. 8, 1913: The dog has remained quite well. Has not shown any symptoms. Laparotomy (one hundred hours after obstruction of intestine). On opening the peritoneum, a small amount of a cloudy fluid escaped. Culture from this fluid remained sterile. The isolated loop was delivered. It was found that the obstructing clamp had completely severed the bowel. The ends of the bowel apparently occluded by adherent omentum. The isolated loop of bowel inside of the clamp was not distended. The content consisted of 10 c.c. of a thin, colorless fluid which was carefully collected. Both ends of the severed bowel were inverted. Abdomen closed.

Of the content of the bowel a culture was taken which remained sterile. Five c.c. of the content were given intravenously to a dog weighing 6.250 gm. The injection was done without an anesthetic. The animal showed no symptoms.

Dec. 9, 1913: The dog with the isolated, obstructed loop eats, but looks sick. Has vomited several times.

Dec. 10, 1913: Dog does not eat. Vomiting.

Dec. 11, 1913: Animal looks slightly better. No vomiting. Laparotomy. On opening the laparotomy wound there was an escape of a purulent fluid. Abscess well localized at region of wound. The obstructed jejunal loop is tremendously distended. Bluish red in color. Peritoneal coat friable. Excised *en bloc*. Abdomen closed.

A culture of the content of the loop was made by aspirating through a sterilized area. The content consisted of 100 c.c. of a thick, viscid, blood-stained material with a slightly disagreeable odor.

Of the fluid, 10 c.c. were given intravenously to a dog weighing 4,500 gm. Local anesthesia. At the end of the injection the animal showed a marked respiratory difficulty. This respiratory difficulty increased and the animal died in thirty minutes. Necropsy showed a marked cardiac dilatation. The lungs were almost solid from edema. The bronchi were filled with a frothy material. No evidence of embolism or thrombosis.

To another animal, 5 c.c. was given intravenously. The animal was observed for one and one-half hours, during which time there was a marked respiratory difficulty. No vomiting. No fluid stools. The animal seemed quite well the following day.

The culture from the obstructed loop content gave an abundant growth on agar. The growth was "plated" on agar plates. The only organism which could be grown was a Gram-negative streptococcus. Subsequent intravenous injection in a dog of a broth culture of this organism did not produce symptoms.

The animal from which the obstructed loop was excised made an uninterrupted recovery.

1. The secretion of a well-draining jejunal loop, after the complete healing of the traumatism, incident to a creation by operative procedure, may produce no symptoms when given, injected intraperitoneally in guinea-pigs or intravenously in dogs, in doses larger than the lethal dose of occluded jejunal loop content.

2. After continued drainage a jejunal loop may become sterile, in which case complete occlusion may persist for a period longer than

is consistent with life with similar occlusion of such loops containing bacteria, without the animal showing symptoms and without the accumulation of a toxic content.

3. After infection of the isolated loop, continued obstruction leads to symptoms and the accumulation of a toxic content.

4. It is significant in this case that the toxic content, when given intravenously to a healthy dog, produced symptoms and a pathologic picture different from that seen after intravenous injection of the content of ordinary occluded jejunal loops, and that the bacteria in the infected loop were not those of the normal intestinal tract. The possibility of the toxins produced differing under different conditions will be referred to again in the discussion of the toxic substance obtained from the incubation of excised segments of jejunum in the thermostat.

#### GROUP VIII.—TOXINS FROM INCUBATION OF SEGMENTS OF INTESTINE IN THE THERMOSTAT

To show that a toxic substance may be produced by the incubation of an intestinal segment which produces symptoms, death, and the same pathologic changes as are produced by the toxin from an obstructed intestinal loop.

EXPERIMENT 66.—(a) From a dog 50 cm. of duodenum and upper jejunum was excised. The lumen of the excised segment was filled with blood and placed in a thermostat at 37 C. and allowed to remain six days. In the autolysis a large amount of gas was formed. The end product was a foul-smelling mass of friable solid tissue, and a reddish-violet liquid. The fluid was separated by filtration through gauze.

(b) Of the fluid, 10 c.c. was injected intravenously into a dog weighing 10,000 gm. at 10 a. m.

12 m.: Animal is up. No vomiting. No fluid stools.

12:30 p. m.: Dog is vomiting.

1:30 p.m.: Dead.

*Necropsy.*—Abdomen contains no free fluid. The intestine is in a state of spastic contraction. The stomach contains several round worms. Mucosa normal. The mucosa of the duodenum and jejunum is swollen and has a deep-red color. The mucosa of the ileum is not so markedly injected.

(c) Twenty c.c. of the fluid was diluted to 40 c.c. with distilled water. Centrifuged ten minutes. The supernatant fluid was filtered through a coarse clay filter, and then through a Berkefeld filter. Culture of the filtrate remained sterile.

Of the filtrate, 20 c.c. was given intravenously to a dog weighing 7,000 gm. at 10 a. m.

11 a. m.: Animal is up. Has vomited once.

1 p. m.: No more vomiting.

2 p. m.: Animal is vomiting.

3 p. m.: Desperately sick. Incessant vomiting. Numerous fluid stools.

4 p. m.: Dead.

*Necropsy.*—Peritoneal cavity normal. Marked congestion of liver and spleen. The stomach is quite normal. The mucosa of stomach is normal. The mucosa of the duodenum and jejunum is swollen and deep red in color. The ileum and colon show a less marked change. The intestinal lumen contains a large amount of mucus.

(d) Ten c.c. of the fluid from the autolyzed loop was diluted to 30 c.c. with distilled water. The mixture was boiled over a free flame ten minutes. A sufficient amount of coagulum formed to preclude the possibility of injecting the material intravenously. The entire material was injected intraperitoneally into a dog weighing 8,200 gm. at 10 a. m.

1 p. m.: Animal is up. No vomiting. No fluid stools.

5 p. m.: Dog has been drowsy during day. No vomiting. No fluid stools.

The following day the animal looked sick. Did not eat. Sacrificed. Necropsy showed the injected coagulum imbedded in the omentum. The peritoneum is injected but shows no evidence of infection. The mucosa of the intestine is quite normal.

EXPERIMENT 67.—(a) From a freshly sacrificed dog, 50 cm. of duodenum and jejunum was excised. The excised loop was distended with 50 c.c. of sterile water and placed in a thermostat at 37 C. for seventy-two hours. The autolysis resulted in the production of large quantities of gas, and finally a putrid mass of friable material and a thin, cloudy fluid. The fluid was separated from the larger pieces of solid matter by filtering through gauze.

(b) 2.5 c.c. of the fluid was given intravenously to a dog weighing 5 kg. at 10 a. m.

11 a. m.: Dog vomited once immediately after recovering from the anesthetic.

11:30 a. m.: Animal very sick. Marked respiratory difficulty. Died.

*Necropsy.*—Lungs show marked edema. Bronchi full of frothy fluid. No evidence of embolism or thrombosis. Heart dilated, filled with blood. The intestines show exaggerated peristalsis. The duodenal mucosa seems a trifle redder than normal.

To prove that the above death was purely a toxic death, 10 c.c. of the fluid was given to another dog weighing 6.2 kg., intraperitoneally. The animal died in thirty minutes, showing the same symptoms and the same pathologic picture after death.

(c) Ten c.c. of the fluid from the autolyzed loop was placed in a thermostat at 60 C. and allowed to remain twenty-four hours. Of this fluid a culture remained sterile. Five c.c. given intravenously to a dog weighing 5,890 gm. at 10 a. m.

12 m.: Animal is up. No vomiting. No fluid stools.

2 p. m.: Dog looks drowsy.

3:30 p. m.: Animal in same condition. No vomiting. No fluid stools. No respiratory difficulty.

The following day the animal had completely recovered.

In Experiment 66, the incubation of a segment of duodenum and jejunum in a thermostat at 37 C. resulted in the production of toxic fluid which, when injected intravenously into a healthy dog, produced symptoms and a pathologic picture identical with that following administration of the contents of an occluded intestinal loop during life. Furthermore, the sterile Berkefeld filtrate acted in a similar manner. The toxic fluid differed from that of occluded duodenojejunal loops in that its toxicity was markedly lowered by boiling.

In Experiment 67, the incubation of a duodenojejunal segment in a similar manner resulted in the formation of a toxic fluid which, when introduced intravenously or intraperitoneally, produced symptoms and a pathologic picture differing from that produced by the administration of the content of an occluded segment of intestine. The toxicity of the

fluid was in this instance markedly changed by heating at 60 C. for twenty-four hours.

These experiments show that the toxic fluid resulting from the autopotrefaction of loops of bowel differs when there is no apparent difference in the condition under which the putrefaction takes place. That the placing of blood in the intestinal loop in Experiment 66, and water in the autolyzing loop in Experiment 67 was not responsible for the difference in the toxic fluid was proven by an additional part of Experiment 67 not described in detail, in which an adjoining segment of jejunum to that excised and distended with water, was excised, filled with blood, and autolyzed the same length of time. The fluid obtained gave the same symptoms and pathologic lesions as that obtained from the loop filled with blood. That the two loops produced a toxic fluid with similar properties suggests that the bacterial flora may be the variable factor.

This characteristic clinical and pathologic picture, seen after the injection of the toxic contents of a loop of obstructed intestine or after the injection of the products of autopotrefaction of an intestinal segment, is identical with that which has been found after the injection of certain ptomain poisons. A preliminary chemical examination, which will be extended, indicates that the toxin may belong to the same group of poisons which was isolated by Faust<sup>5</sup> in his study of the ptomains.

It is also interesting to note that the character of the putrefactive process is different from that seen in the lumen of the bowel after simple occlusion of an isolated loop in the living animal. For example, in the former there is a tremendous amount of gas produced which is never seen in the latter. In case the arteries to an isolated, obstructed loop are tied, gas is formed. We have never seen gas in an occluded jejunal loop in which the veins were tied.

GROUP IX.—EXPERIMENTS TO TEST THE RELATIVE IMPORTANCE OF THE  
TWO FACTORS, PRODUCTION OF TOXIN AND ABSORPTION OF  
TOXIN, IN THE CAUSATION OF SYMPTOMS

EXPERIMENT 85.—Dog. Laparotomy. Tape tied around duodenum below pancreatic duct opening. Another tape tied around jejunum, 20 cm. below duodenojejunal junction. Thirty c.c. of the content of an isolated obstructed loop of jejunum of seventy-two hours' duration injected into the lumen of the occluded segment of bowel. Gastro-enterostomy, distal to distal tape. Abdomen closed.

Twenty-four hours: Dog is up. Does not eat.

Forty-eight hours: Animal dead. Necropsy shows the occluded loop tremendously distended with foul fluid.

5. Faust: Arch. f. exper. Pathol. u. Pharmacol., 1904, li, 248.

EXPERIMENT 86.—Dog. Laparotomy. Two tapes tied tightly around the jejunum so as to include from 30 to 40 cm. of its proximal portion. Veins in the mesentery of obstructed segment ligated. Abdomen closed.

Seven hours: Animal vomiting.

Twenty-two hours: Died.

EXPERIMENT 87.—Dog. Laparotomy. Two tapes tied tightly around high jejunum so as to include between them from 30 to 40 cm. of bowel. Seventy-five c.c. of the toxic content from an obstructed jejunal loop of seventy-two hours' duration injected into the lumen of the bowel between the tapes. The veins in mesentery of the occluded loop ligated. Abdomen closed.

Three hours: Animal vomiting.

Nineteen hours: Animal died.

These experiments show that the introduction of toxic fluid into the lumen of occluded intestinal loops with and without strangulation does not materially decrease the length of life after intestinal obstruction. In Experiment 85, in which several times the lethal dose of toxic fluid for intravenous administration was introduced into the occluded loop, the animal lived forty-eight hours. Animals having the same operation with no toxic fluid usually live forty-eight to seventy-two hours. In Experiment 87, in which a large amount of toxic material was introduced into the lumen of a strangulated loop of bowel, the length of life was only three hours less than in Experiment 86, in which the same operation was done except no toxic material was introduced into the obstructed bowel. Hence in the causation of symptoms, the factors leading to the absorption of the toxin are relatively more important than those of the production of the toxin. This fact has an important bearing on the surgical treatment of intestinal obstruction.

#### SUMMARY

Certain of these experiments were repetitions of those of other investigators. They were necessary in order to confirm or refute the previous observations and to form a complete series from which conclusions could be drawn concerning the symptomatology and pathology of intestinal obstruction, as well as the reasons for the conflicting views which exist regarding the origin and nature of the toxin in intestinal obstruction and the way in which it is absorbed.

This study justifies the following conclusions:

1. In intestinal obstruction, the content of the obstructed bowel contains a toxin which, when absorbed in sufficient amounts, produces definite symptoms and pathologic lesions and death.
2. The toxins are the result of bacterial growth. They are not specific for any part of the intestinal tract, and may be formed in the gall-bladder.
3. The chemical and physical characteristics of the toxic substance may vary with the length of time which the obstruction has existed as

well as with the different conditions under which the obstruction occurs.

4. This toxin may enter the circulation by way of the thoracic duct.

5. Death after intestinal obstruction is the result of a toxemia which may be independent of infection of the peritoneal cavity or general circulation.

6. This toxic substance does not pass through a normal mucous membrane.

7. In the production of symptoms the factors which make this absorption possible are more important than the factors which produce the toxin.

8. Interference with the circulation of the obstructed intestine is an essential factor in allowing this abnormal absorption.

9. Simple obstruction of a segment of duodenum or jejunum results in earlier and severer symptoms than similar obstruction of a segment of ileum because the secretion into the lumen of the former leads to rapid distention and circulatory disturbance in the bowel wall.

10. The symptoms and pathologic lesions following the intravenous administration of the contents of a segment of bowel after obstruction are the same as those described resulting from intravenous injection of certain of the ptomain poisons.

11. In the surgical treatment of cases of intestinal obstruction, that part of the intestine with a mucous membrane which has been so damaged as to permit of abnormal absorption should be resected rather than drained.



# A WORKING HYPOTHESIS OF HEMOGLOBIN PIGMENT METABOLISM \*

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In the following pages arguments in favor of the view that hemoglobin pigment is produced and decomposed in the liver are presented.

This view was suggested by work which has already been published from this laboratory, and to some extent the evidence in favor of it is drawn from that source. New work has been started on the basis of this hypothesis along several lines, but there are so many questions raised, which circumstances prevent us from attempting to answer, that it seemed better to present what evidence we have at present.

It is claimed that those data which we already possess are harmonized and rendered intelligible by the adoption of this view, and that there is sufficient evidence to justify its acceptance as a working hypothesis.

As it was in the hope that applications to clinical medicine might be found that the subject was approached, special stress has been laid on the possibilities opened up along these lines.

## THE DECOMPOSITION OF HEMOGLOBIN PIGMENT

One of the outstanding features of blood metabolism is its intensity, the rapidity with which it is continually being broken down and rebuilt. We have no means of measuring exactly the rate of hemoglobin decomposition and regeneration, but from the data which we possess it has been calculated that not less than 7 per cent. of the total red blood-cells are daily disintegrated in the body. Each individual red blood-cell, therefore, lives for about fourteen days. What is then its fate?

It would seem that there are special cells distributed throughout the body whose function it is to remove decrepit red blood-cells from the blood-stream. These are endothelial phagocytic cells which may differ considerably in morphology, but are united in possessing certain functional capacities. Thus they take up finely suspended "vital" stains, or colloidal metallic solutions, when these are injected into the blood-stream, and they have some connection with cholesterin metabolism,

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\* From the Laboratory of the Division of Medicine, Stanford University Medical School.

for the doubly refractile droplets characteristic for this substance may be demonstrated within them.

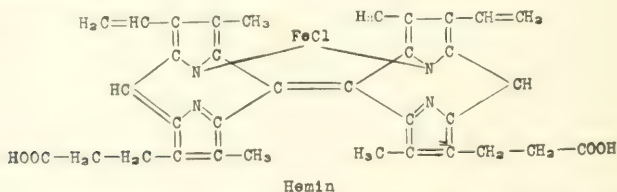
They are situated in the sinuses of the spleen especially, to a less extent within the capillaries of the lymphatic glands and bone-marrow, and stretching across the lumen of the capillaries they constitute in the liver, the Kupffer or stellate cells.

The cells of this type may be seen to engulf the red blood-cells, and, as the work of Bain<sup>1</sup> and of Paton and Goodall<sup>2</sup> indicates, it is the old and damaged corpuscles which are thus taken up. Within or near the endothelial cell the corpuscle breaks down. There is evidence that in the spleen at least the hemoglobin which is thus set free is excreted into the blood plasma. And the special function of the Kupffer cells is not only to phagocytose red blood-cells, but also to take up the free hemoglobin which is brought to it in the form of a fine emulsion from the splenic vein. The droplets of hemoglobin have been seen to pass from the Kupffer cells into the liver cells.

This liberation of hemoglobin from the corpuscles is the first step in the process of hemoglobin pigment decomposition. The next is probably the detachment of the pigment moiety hemochromogen—from the protein globin. Hemochromogen can be readily separated from globin by hydrolysis outside the body, and by the action of hydrochloric acid, a stable substance—hemin—is produced with altering its essential

constitution, in which four pyrrol nuclei  $\begin{array}{c} \text{HC} \text{-----} \text{CH} \\ || \qquad \qquad || \\ \text{HC} \qquad \qquad \text{CH} \\ \diagdown \qquad \diagup \\ \text{NH} \end{array}$  are linked to

an atom of iron.

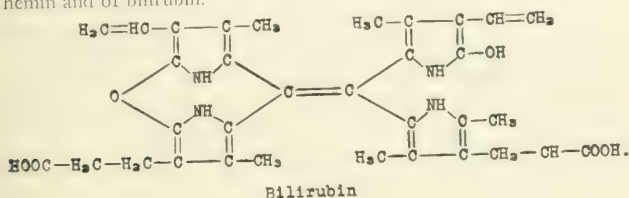


The hemoglobin pigment which is thus set free is converted into bilirubin. This is the most important change which it undergoes, but it is the one about which we know least. No one has succeeded in reproducing the necessary reactions outside the body, either in per-

1 Bain: Jour. Physiol., 1903, xxix, 352.

2 Paton and Goodall: Jour. Physiol., 1903, xxix, 411.

fusion, autolytic or digestion experiments, and there is consequently a gap in our knowledge of the chemical processes which are involved. The proof that hemoglobin pigment is the source of the formation of bilirubin rests on experiments which show that when hemoglobin pigment is injected into the blood-stream it produces an almost quantitative increase in the bilirubin excreted in the bile. But although we do not understand the manner in which the conversion is accomplished, we can see the extent and nature of the change by comparing the formulae of hemin and of bilirubin.



The four pyrrol nuclei are still present, but the iron has gone, and there is more oxygen present.

Where does the change of hemoglobin pigment into bilirubin take place?

A short time ago there would have been few who would have had any hesitation in maintaining that it was in the liver cell alone that this transformation occurs, although it was admitted that in old blood extravasations a substance indistinguishable from bilirubin was occasionally found.

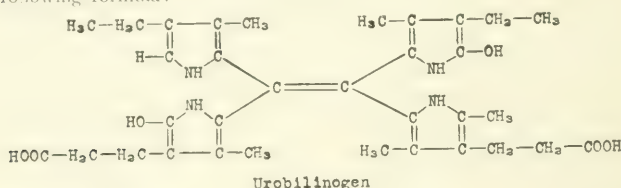
There is still no doubt that the liver cell under normal conditions is the place where bilirubin is formed. But since the work of Whipple and Hooper<sup>3</sup> and of McNee<sup>4</sup> has appeared, it must be admitted that in all probability, bilirubin can be formed elsewhere, for they have succeeded in producing icterus in the absence of practically the entire liver. This extrahepatic icterus of Whipple and of McNee's experiments finds its clinical counter-part in the cases of hemolytic jaundice in which with no diminution or hindrance to the excretion of bilirubin in the bile, there is, nevertheless, a more or less marked degree of icterus. Widal, some years ago, pointed out that the discarded theory of hematogenous jaundice was the only one which could account for such cases. And, as in Banti's disease, we may reasonably postulate a hyperactivity of the hemolytic function of the endothelial phagocytic cells, so also there is some evidence for the hypothesis that in "hemolytic jaundice" con-

3. Whipple and Hooper: Jour. Exper. Med., 1913, xvii, 593 and 612.

4. McNee: Jour. Path. and Bacteriol., 1914, xviii, 325.

ditions are present which allow this group of cells to assume in part the function of bilirubin formation.

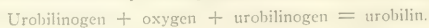
The final stage in the decomposition of hemoglobin is the conversion of bilirubin into urobilinogen. This is an entirely extracellular process which takes place in the intestine. There the bilirubin begins to undergo a change which is the reverse of the process by which it was formed from hemoglobin pigment, in that it is essentially a reduction. Urobilinogen can be made from bilirubin outside the body by the use of strong reducing agents, and its formation in the intestine is no doubt favored by the relative absence of oxidation reactions there, but as yet we know little about the conditions under which it is produced. Hans Fischer and Röse<sup>5</sup> have succeeded recently in isolating it and give the following formula:



Urobilinogen contains a hydrogen atom attached directly to a carbon atom of one of the pyrrole rings and on account of this grouping, it reacts with paradimethylaminobenzaldehyd to form a red pigment which has a characteristic absorption spectrum.

By making use of this reaction, changes in the amount of urobilinogen in a solution under different conditions can be readily followed. Such studies immediately show that urobilinogen is not an end-product of hemoglobin metabolism. It is an extremely unstable body which readily takes up oxygen, and loses the capacity to form the red pigment with paradimethylaminobenzaldehyd. In its place there appears the pigment urobilin which has certain spectroscopic characteristics which allow of rough estimation.

The studies of Hans Fischer and Meyer-Betz<sup>6</sup> indicate that the formation of urobilin depends on the union of two molecules of urobilinogen under the influence of oxygen, a reaction analogous to the production of indican by the oxidative polymerization of indoxyl sulphates. The reaction may be expressed schematically thus:



The reduction of bilirubin to urobilinogen in the intestine is complete. No evidence could be obtained that the conversion stops in man

5. Fischer and Röse: *Ztschr. f. physiol. Chem.*, 1914, lxxxix, 255.

6. Meyer-Betz: *Ergebnd. inn. Med. u. Kinderkr.*, 1913, xii, 733.

at substances intermediary between bilirubin and urobilinogen, although in the dog it would seem probable that this occurs. But the process does not stop with urobilinogen, so that human stools practically always contain a varying amount of urobilin before they are passed. As soon as the stool is exposed to the action of the oxygen of the air, the formation of urobilin goes on more rapidly, especially under the influence of light. This explains the familiar fact that after a stool has stood for some time, it is darker on the surface than in the central unexposed parts. The colorless urobilinogen has been turned into the brown pigment urobilin.

Should we then look on urobilin as the end-product of hemoglobin metabolism? We cannot do so if we define an end-product as a final cleavage product which cannot be made use of or further changed in the body.

Urobilin is not a fixed substance. Its instability has, so far, not allowed of the determination of a constitutional formula, and we do not know with certainty the products of its change. But we do know that the same conditions which favor the conversion of urobilinogen into urobilin also bring about the disappearance of the urobilin itself. I believe that this is a very important fact and that it is the key to the understanding of the whole subject. It will be returned to in considering the formation of hemoglobin.

In summing up our knowledge of the decomposition of hemoglobin pigment we may conclude that, under normal conditions, hemoglobin is liberated from the old red blood-cells by phagocytic endothelial cells: that the hemoglobin thus set free passes into the blood plasma and is taken up by the Kuppfer cells which pass it on to the liver cells. Here the pigment is separated from globin, and after removal of iron and undergoing intramolecular changes which involve the addition of oxygen, is converted into bilirubin. The bilirubin passes into the intestine, and is reduced to urobilinogen, which again in part is polymerized to urobilin.

#### THE FORMATION OF HEMOGLOBIN

Is the animal organism capable of forming for itself the keystone in the structure of hemoglobin pigment — the pyrrol nucleus — or is it dependent on the ingestion of preformed pyrrol nuclei in the food?

A new formation of pyrrol within the body has never been demonstrated. That does not mean much, but on the other hand there is nothing inherently improbable in the conception that in the last resort the body has to rely on sources outside of itself for the formation of hemoglobin. We have the analogy of the benzene ring, which can be evolved only by processes peculiar to the vegetable organism, although

it forms an essential part of many of the structures of the animal body (Baumann<sup>7</sup>).

Apart from blood and chlorophyll, the only food constituent which is known to contain the pyrrol nucleus is the amino-acid, tryptophane, a body which is found in considerable amounts in nearly all proteins.

Thanks to the work of Osborne and Mendel,<sup>9</sup> we are in possession of exact and detailed data on the effect of a diet free from blood, chlorophyll and tryptophan on the weight and growth of rats. They show conclusively that under these conditions the body tissues cannot be maintained. There is a progressive loss of weight, which can be at once arrested by the addition of small quantities of tryptophan to the food. They make no mention of anemia, but even if there were no anemia, the possibility of hemoglobin formation by pyrrol synthesis within the body would not be proved, for the total quantity of tryptophan in the body is large, and it is conceivable that with a reduction of the rate of hemoglobin metabolism to a minimum, enough hemoglobin might be formed at the expense of pyrrol liberated from the wasting tissues. This seems to be a rather strained interpretation, however, and it is true that the absence of any note as to pronounced anemia in these observations and in the numerous records of complete starvation experiments, is a point which speaks for the capacity of the body to produce pyrrol for itself, even though it does not by any means prove it. We are planning work in connection with this point, but in the meanwhile it may be left on one side.

So far as the question at issue is concerned, it is enough to know that even if the organism can synthesize pyrrol, this product must of necessity pass through many complicated changes before it is finally welded into the intricate molecule of hemoglobin pigment.

On the other hand, in the urobilinogen in the intestine we have a substance in which the pyrrol nuclei are already linked together in their proper relationships to one another. All that we have learned of the economy of natural processes would tend to make us expect to find that urobilinogen would be used in the synthesis of hemoglobin pigment.

We have proof that a considerable part of the urobilinogen daily formed is not lost to the body by being excreted in the stools, but is absorbed from the intestine in the portal blood-stream. This was proved in Müller's classic experiment where he showed that the urobilinogen which appears in the urine has its origin in the intestine. This has been amply confirmed most recently and most directly by Fischer and Meyer-Betz.<sup>10</sup> With the absence of bilirubin from the

7. Baumann: *Ztschr. f. physiol. Chem.*, 1886, x, 123.

9. Osborne and Mendel: *Jour. Biol. Chem.*, 1914, xvii, 325.

10. Fischer and Meyer-Betz: *Ztschr. f. physiol. Chem.*, 1911, lxxv, 232.



intestine, no urobilinogen is formed, and none can be detected in the urine until bile or urobilinogen are given by mouth. The quantity of urobilinogen and urobilin in the stools is less than the theoretical quantity which should be obtained from the amount of bilirubin entering the intestine. The deficit is absorbed into the blood.

With the recognition of this fact, however, we come to the end of what is generally accepted as established. The suggestion has of course been made that the absorbed urobilinogen is utilized in the formation of hemoglobin, but no hypothesis has been advanced as to the manner of its utilization or as to its effects on urobilinogen excretion.

Wilbur and Addis<sup>11</sup> not long ago published a paper on "Urobilin" which contained the results of quantitative estimations of urobilinogen and urobilin under physiological, pathological and experimental conditions. Since that paper was written some important work of a purely chemical nature has appeared which throws light on some obscurities and difficulties which were encountered in presenting a theory of urobilinogen excretion.

It is, therefore, now possible to put forward a working hypothesis of hemoglobin metabolism which brings these observations into line, which formulates the relationship between hemoglobin decomposition and formation, and which has a practical application, in that it serves as a theoretical support of a formerly more or less empirical method of recognizing disturbances of liver action.

Urobilinogen is found only in traces in normal urine. But in disease there are two groups of conditions in which large amounts of urobilinogen are excreted in the urine.

In one there is an increased destruction of red blood-cells within the body. Malaria is the typical example. In such cases the proof of an unusual degree of blood destruction is found in the greatly augmented quantity of urobilinogen and urobilin in the stools.

In the other group the amount of urobilinogen and of urobilin in the stools is within the normal limits of variation or is decreased, and there is no evidence of excessive blood destruction. The majority of these cases are outspoken examples of disease of the liver — the initial stages of catarrhal jaundice, the toxemic stage of advanced cirrhosis, suppurative cholangitis, etc. — especially conditions in which the liver as a whole is involved, whereas in such local disease as carcinomatous metastases no very marked urobilinuria may be found. Great increase in urobilinogen excretion is also evident in some cases of acute infections such as lobar pneumonia, where a diffuse liver involvement is probable.

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11. Wilbur and Addis: THE ARCHIVES INT. MED., 1914, xiii, 235.

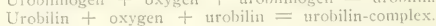
On the whole, the clinical evidence is very strong that the presence of considerable amounts of urobilinogen in the urine is associated with liver disturbance, if marked increase in hemoglobin disintegration can be excluded.

Since the urobilinogen in the urine of these cases of liver disease is known to have its origin in the intestine, the current theory is that the normal liver absorbs the urobilinogen brought to it in the portal vein, whereas the diseased liver allows it to pass into the general circulation from which it is excreted by the kidneys. But in what form does the normal liver absorb urobilinogen? Not as such, for none can be extracted from the liver tissue. Not as urobilin, for this substance also is absent. It does not simply pass through the liver into the bile, for only traces of urobilinogen and urobilin are found there under normal conditions.

It is not even brought to the liver as urobilinogen, for none can be found in the blood, not even when large amounts of urobilinogen are being excreted in the urine.

Obviously, therefore, urobilinogen when it is absorbed is changed into some substance which has not been identified.

It will be remembered that urobilin is formed under the influence of oxygen by the union of two molecules of urobilinogen. But if a solution of urobilin is left exposed to air and light it will steadily decrease in quantity, just as the amount of urobilinogen diminishes when its solutions are left under the same conditions. The parallelism between both phenomena is so marked as strongly to suggest that both are the result of the same process, and that the disappearance of urobilin is simply a continuation of the reaction which is known to underlie the formation of urobilin from urobilinogen, namely, a polymerization. The unidentified substance formed might be called urobilin-complex, and the process might be expressed thus:



The following experiment is an example of many which have been carried out in connection with this point.

An acid alcohol extract of a stool after the addition of zinc acetate in absolute alcohol was found to contain urobilinogen to the dilution value of 17 and urobilin to 20 in each 10 c.c. volume. It was left exposed to the air under the action of diffuse room light. After seven hours samples were removed and separate estimations of urobilinogen and of urobilin were made. The urobilinogen had entirely disappeared, but the urobilin had increased to a value of 40; that is to say, the urobilinogen had been converted into urobilin. But the increase in urobilin would have been still greater if another process had not been

proceeding coincidentally, i. e., the polymerization of the urobilin molecules to form the urobilin-complex. This process we have no means of measuring except by the disappearance of urobilin which is shown in the chart to be progressive, though not regular, since the decrease was more rapid during the day-time under the action of light, than at night.

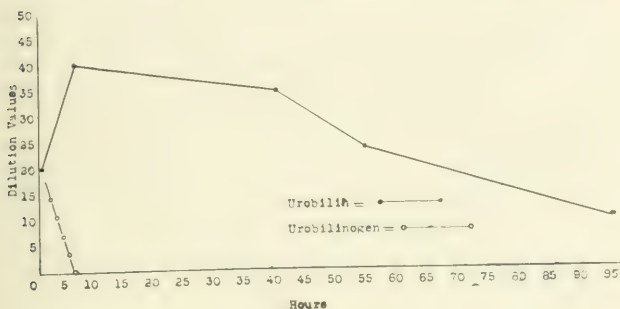


Chart 1.—The dilution values for urobilinogen and for urobilin depend on their respective light-absorbing capacities. Since urobilin has not been isolated its power in this respect cannot be determined with exactitude, and its dilution value must not be assumed to be directly comparable with that of urobilinogen. As a matter of fact, if equal weights of the two substances could be compared, it would be found that the dilution value of urobilin was higher than that of urobilinogen.

In the numerous efforts which have been made to find urobilinogen or urobilin in the blood, nothing has been learned which is in opposition to this hypothesis, and there are some points which indirectly support it.

The blood of patients in whom there is a large excretion of urobilinogen in the urine has never been found to contain any urobilinogen. Urobilin has been found in a few cases. But it is noteworthy that a common factor in such cases is that the patients have been cyanosed. Almost all of them have been cases of lobar pneumonia in the terminal stages with dilated right hearts and marked cyanosis. Now it was shown some years ago by Roth and Herzfeld<sup>12</sup> that when urobilin is added to the blood *in vitro* it disappears. If it is added to serum alone, however, or even to blood through which carbon dioxid has been passed, it can be recovered. It would seem that both the clinical and the experimental findings may be explained on the assumption that the formation of the urobilin-complex is greatly hastened by oxyhemoglobin, so that it is only when the oxygen of the blood is diminished that urobilin can exist in the blood-stream.

12. Roth and Herzfeld: *Deutsch. med. Wchnschr.*, 1911, xxxvii, 2129.

We may therefore amplify the theory of urobilinogen excretion in the urine of cases of hepatic disease by explaining it as being due to the incapacity of the liver to absorb the urobilin-complex brought to it from the intestine, so that part of this substance escapes past it into the general circulation and reaches the kidneys.

The kidneys excrete only urobilinogen, never urobilin, or urobilin-complex. Probably because of their size, these molecules have to be reduced to urobilinogen before they can pass through the kidney cells. To judge from the prompt appearance of urobilinogen in the urine after injury to the liver, this is a function which the kidneys accomplish without much difficulty, and it would seem reasonable to argue from the fact that only very small traces of urobilinogen are found in the normal urine that the healthy liver is capable of holding almost all the urobilin-complex which is brought to it. The large amounts which may be excreted when the liver is diseased is some indication that the quantity thus absorbed may be not inconsiderable, although it cannot, as we shall see, be taken as a measure of the normal capacity of the liver.

One of the observations of Wilbur and Addis which could not at the time be fully understood was the extraordinary variations in the quantity of urobilinogen in the urine at different periods of the day. Charts 2 and 3 show the quantities of urobilinogen excreted every two hours in a case of bronzed diabetes.

This case was observed over a long period, and at no time was there any relation between the excretion of urobilinogen and of water, urea, chlorids or sugar in the urine. Every night the amount of urobilinogen was greatly decreased as compared with the amount which was passed during the day, but when the patient's habits were reversed and he slept during the day and remained awake and took his meals through the night, the quantitative relationship between the day and night urobilinogen was also reversed. This cannot be satisfactorily explained simply by variations in the absorption of urobilinogen derived from bilirubin, for this is a process which occurs mainly in the large intestine, and there is no reason to believe that there are any sudden changes either in the formation or in the absorption of this urobilinogen.

The study of the urobilinogen and urobilin content of the bile also gave results whose significance was obscure. In post-mortem bile wide variations were found, from traces too small to estimate to very large quantities, and there was apparently no relation between the amount in the feces and in the bile. In following the daily variations in the urobilinogen and urobilin in the bile discharged from gall-bladder fistulas in patients in whom the gall-bladder had been drained for gall-stones or cholecystitis, it was demonstrated clearly that during the periods

when the patient was feverish and toxemic the quantity of urobilinogen and urobilin was greatly increased, even though little bile was reaching the intestine, and there was consequently little urobilinogen in the stools.

These anomalies in the urobilinogen excretion by way of the urine and bile were not to be explained by any of the current views, and they were simply recorded as facts which any future theory would have to reckon with. The following hypothesis does elucidate not only these facts, but also puts the other data which have been accumulated in their proper place as parts of an ordered sequence of events.

The liver is the central and regulating organ in the metabolism of hemoglobin, not only of its decomposition, but also of its formation. Hemoglobin is converted by the liver into bilirubin. Bilirubin is excreted in the bile into the intestine and is changed to urobilinogen, part of which is excreted in the stools and part absorbed into the portal blood-stream. The urobilinogen in the blood is polymerized to the urobilin-complex. The urobilin-complex is practically all taken up by the liver, but a small amount gets past into the general circulation and is decomposed in the kidneys to urobilinogen and excreted.

But what happens to the greater part of the urobilin-complex which under normal conditions does not get past the liver?

The idea that urobilinogen may be stored in the liver in the polymerized form of urobilin-complex, just as sugar is stored as glycogen, comes at once to the mind as a possibility. Now we know something about the capacity of the liver in storing glycogen, and something also about its power to contain fat, so that it would not be surprising to find that the liver exercised a similar function in connection with hemoglobin metabolism. On the other hand, we also know that the storage capacity of the liver is one of the last of its functions to be disturbed in disease. No matter how disorganized a liver may be, so long as life continues it retains the power to hold glycogen. The relative freedom of the liver from glycogen which is frequently seen post mortem, is the result of diminished intake and increased utilization of sugar, rather than of any inability of the liver to store glycogen, for it is not relatively passive, but active functions which are the first to fail.

But it is preeminently the failure to hold the urobilin-complex which is the first indication of hepatic disturbance. For instance, any toxemic condition, such as that which accompanies an acute tonsillitis, is usually followed by a marked increase in the excretion of urobilinogen in the urine. The liver as a whole is no doubt adversely affected in such conditions, but not as a rule sufficiently to disorganize any of its other functions to an extent which permits us to recognize any abnormality.

Again, it is a well-known fact that if there is need for it the liver can make room for enormous quantities of glycogen, as much as 18 per cent. of the liver weight may be pure glycogen, after large quantities of carbohydrates have been taken.

But even apart from disease of the liver, the limits of its capacity to hold the urobilin-complex are relatively narrow. Since so large a proportion of the total hemoglobin of the body is daily decomposed, it is surprising to find what a relatively small increase in the amount of hemoglobin destroyed is sufficient to lead to the escape of part of the urobilin-complex past the liver.

The conception of a simply passive storage of urobilin-complex in the liver seems to me to be entirely inadequate to account for these facts. It would rather seem that the liver had some active function to perform in connection with the urobilin-complex — a function in which many factors were concerned, which therefore could not be made to work overtime simply by an increase in the urobilin-complex alone, and so intricate that unfavorable circumstances acting on the liver as a whole might readily slow or stop it.

A function which certainly answers this description is the syntheses of hemoglobin-pigment, and the suggestion is put forward that the liver rearranges the atoms in the urobilin-complex to some nearly complete stage in hemoglobin pigment formation in which it is ready for assimilation by the erythroblasts of the bone-marrow.

Such an idea does not find ready acceptance, because one is accustomed to look on the bone-marrow as the site of hemoglobin formation. But so far as I have been able to find the only reason for this belief is the fact that it is possible to trace there all the stages between the early erythroblast, with apparently no hemoglobin, up to the fully formed erythrocyte full of hemoglobin. But that does not prove that the pigment is actually formed within these cells. When hemoglobin is in a coagulated form (Miura<sup>13</sup>) it no longer has its characteristic color or staining reactions, and it may very well be that the erythroblast simply has the capacity to absorb hemoglobin or hemoglobin pigment in some physically altered form, and that the apparent growth of hemoglobin which can be observed within this cell as it develops, is simply a gradual reduction of colorless hemoglobin to the form with which we are familiar.

Looking at the matter simply from the point of view of probability, one would be more ready to believe that such an intricate matter as the synthesis of hemoglobin would be carried out in highly specialized cells such as the liver cells rather than in the undeveloped protoplasm of the

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13. Miura: *Biochem. Ztschr.*, 1913, xlix, 137.



early erythroblasts. In this connection it will be remembered that Goldmann's<sup>14</sup> work shows that the early embryo is incapable of producing hemoglobin for itself and has to receive it fully formed from the mother through the placenta, and that in the hen's egg Hugonneng and Morel<sup>15</sup> found a substance which they termed hématovine, which is simply hemoglobin in a slightly modified form. Until the liver is functioning the organism is incapable of synthesizing hemoglobin from pyrrol nuclei.

This conception of the liver as the site of hemoglobin formation is the only one which can account for the unexplained facts which have been mentioned in regard to urobilinogen excretion in the bile and urine.

When this function of the liver is in abeyance the urobilin-complex brought to it cannot be used. It is therefore excreted again into the bile in the form of urobilin and urobilinogen. Thus in cases of gall-bladder fistula in which through bacterial infection the liver was damaged, a large amount of these substances was found in the bile, an amount which bore no relation to the small amounts of urobilinogen found in the stools. On the other hand, when the infection was overcome and the liver recovered, only traces of urobilinogen and urobilin were found, even when enough bilirubin passed into the intestine to lead to the excretion of considerable amounts of urobilinogen and urobilin in the stools. The urobilin and urobilinogen content of the bile depends, therefore, rather on the capacity of the liver to use the urobilin-complex than on the amount which is brought to the liver from the intestine.

There is another point, however, which has to be borne in mind. Urobilinogen is, relatively to urobilin, a readily diffusible substance, and therefore the urobilinogen which is excreted in the bile is in great part rapidly absorbed from the small intestine. In this way the same urobilinogen may continue to circulate between the liver and intestine so long as the liver is incapable of using the urobilin-complex. If in addition urobilinogen derived from the intestinal decomposition of bilirubin is also being absorbed from the large intestine, it can be seen that the quantity of urobilinogen and urobilin in the bile may become very large, as in fact we have found in such cases. Under these circumstances the portal blood-stream will soon become saturated with urobilin-complex and the excretory capacity of the liver be overtaxed, so that part of the urobilin-complex escapes past the liver into the systemic circulation from which it is removed by the kidneys. It is well

14. Goldmann: *Aussere und innere Sekretion des gesunden und kranken Organismus.*, 1912, p. 30.

15. Hugonneng and Morel: *Jour. physiol. et de path. gén.*, 1906, viii, 391.

known that the excretion of bile into the intestine is not constant, but is much augmented at the times when pancreatic secretion occurs. Immediately after the entrance into the duodenum of a bile rich in urobilinogen, there is a rapid absorption of urobilinogen in the form of

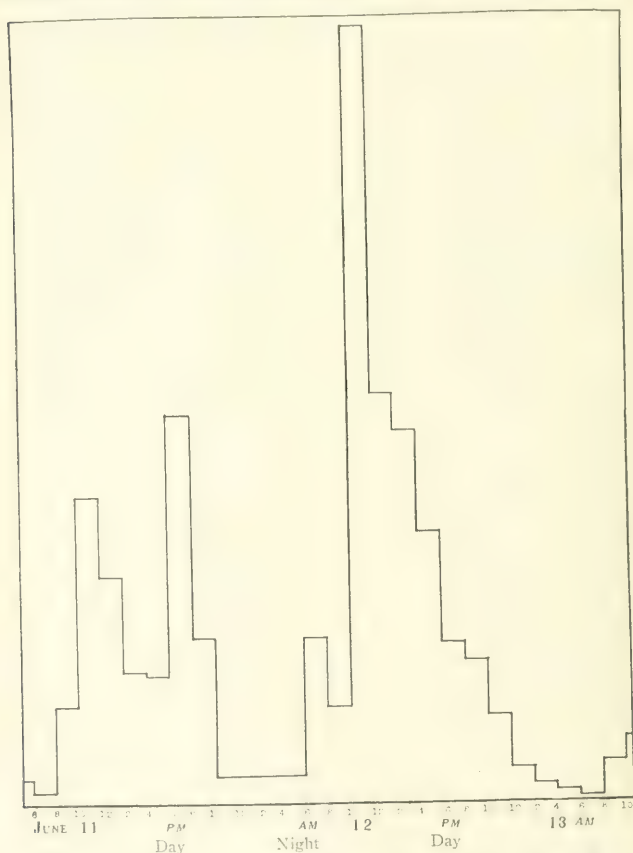
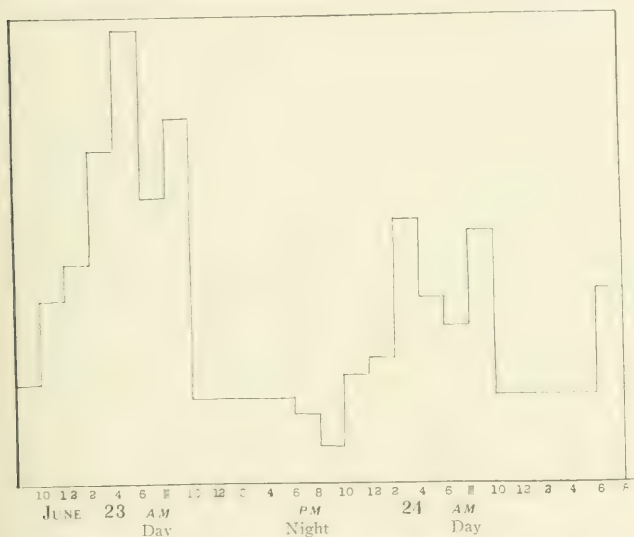


Chart 2.—Excretion of urobilinogen June 11 and 12. Food taken during day time.

urobilin-complex, the liver is overflowed, and as a consequence there is a sharp rise in the urobilinogen excretion in the urine. That the marked excess of urobilinogen excreted during the day is in fact to be

associated with the processes of digestion, is shown by the inversion of this relationship when the food is taken during the night, as is shown in the curves of two-hourly urobilinogen amounts in the case of bronzed diabetes.

The constancy with which any generalized interference with the liver is followed by urobilinogenuria, even though it may be a com-



of amino-acids does not determine any increase in the reactions involved in the synthesis of new tissue. These reactions require an exact balancing of different constituents, and so any excess of amino-acids above what are required by the tissues is decomposed and excreted as urea in the urine. This parallels the conditions in hemoglobin pigment metabolism, when there has been an excessive formation of bilirubin and as a consequence more of the urobilin-complex is carried to the liver than is necessary for hemoglobin formation. The excess is at once broken down into urobilin and urobilinogen and excreted in the bile.

On the other hand, the flooding of the portal circulation with the urobilin complex, which occurs when the formation of hemoglobin in the liver is in abeyance, has no parallel in the protein metabolism of the tissues. The urobilin and urobilinogen into which the unused urobilin-complex is decomposed as it is excreted through the liver cells, is quickly reabsorbed from the small intestine. With it comes an added increment of urobilinogen from the decomposition of bilirubin. So long, then, as the liver ceases to make use of the urobilin-complex it will heap itself up in the portal circulation, until the blood becomes so saturated with it that the liver can no longer absorb all of it and part escapes into the general circulation to be decomposed in the kidney and excreted as urobilinogen in the urine. In the general protein metabolism there is no such reabsorption of the products of decomposition in order that they may again be used in the building of the tissues, and therefore no accumulation in the blood-stream when anabolism is hindered.

The fact that the hemoglobin-forming function of the liver may show signs of failure, while its other functions, such as, for instance, the capacity to convert sugar into glycogen, are still carried out without difficulty, is explicable when the sensitiveness to any unfavorable change in environment of the comparable synthetic processes concerned in the growth and maintenance of the body tissues, as compared with the relative stability of the general carbohydrate and fat metabolism, is remembered. Bacterial infections, many gastro-intestinal conditions, sometimes even merely psychic disturbances, may lead to a cessation of the maintenance and growth of the protoplasm of the body, even though there are no signs of interference with the power of the tissues to store and utilize carbohydrates and fat. Just as the delicate and intricate reactions on which the building of the nitrogen-containing structures of which the body is composed are the first to be disorganized of all the processes in the general metabolism of the tissues, so in the special metabolism which is carried on in the liver, the rearrangements of the pyrrol nuclei required in the synthesis of

hemoglobin, may be interfered with before the other hepatic functions are involved.

If hemoglobin pigment formation is carried on in the liver and is so easily disturbed, it would follow that any continued interference with this function should be followed by anemia.

It must be borne in mind that here, as in all other important functions of the body, a wide margin of safety may be expected. No doubt the liver is capable, if need be, of producing a much larger amount of hemoglobin than is usually required of it, so that only a fraction of the total liver substance may be sufficient to carry on the work of the whole. In Eck-fistula dogs anemia is not a constant finding, so that it would seem that a relatively small part of the liver may be sufficient if it is functioning normally. It is to be remembered, however, that Enderlen and Magnus-Alsleben<sup>16</sup> have shown recently that the amount of normal liver in an Eck-fistula dog is much greater than is usually assumed, for the hepatic artery rapidly acquires the capacity to give sufficient blood to a great part of the liver. Nevertheless, we know that purely local liver lesions are not necessarily accompanied by urobilinuria and we may assume that so long as a part remains active — how large a part is necessary we do not know — no anemia from decrease in the formation of hemoglobin will result.

The cases in which anemia may be expected are those in which the liver as a whole is involved.

What then are the clinical conditions in which a generalized lesion of the liver exists?

Acute yellow atrophy is not a diffuse lesion. Patches of liver tissue remain and when the patient does not die at once, are sufficiently healthy to grow in size and to divide with great rapidity. Nor is there always any general involvement of the liver cells in conditions grouped under the term cirrhosis, except in the terminal stages.

It is in the cloudy swelling which accompanies severe general infections, such as pneumonia, that one comes nearest to a lesion affecting the liver universally. It is in such cases that one finds large amounts of urobilinogen in the urine, amounts which rise and fall with the course of the disease. It is in such cases, too, that an anemia develops, which becomes more evident the more protracted and severe the infection.

As it is generally understood, the term "anemia" signifies either a decrease in the number of red blood-cells per cubic millimeter of blood, or a fall in hemoglobin percentage, or, as is usual, both combined in varying degree.

16. Enderlen and Magnus-Alsleben: *Ztschr. f. d. ges. exper. Med.*, 1914, iii, 223.

The word, then, covers changes in two substances which under the hypothesis which has been put forward, are genetically distinct, the red blood-cell stroma which is derived from the bone-marrow and its content, the hemoglobin pigment which comes from the liver. Under widely varying physiological and even pathological conditions there is a considerable degree of constancy in any individual in the number of red blood-cells and in the percentage of hemoglobin. Whenever a constant is found we must have a regulating mechanism by which it is maintained. But our methods are as yet too crude to carry us very far in the study of the method of its control. The clinical blood-count and hemoglobin estimation are quite inadequate to give us any idea of the number of red blood-cells and amount of hemoglobin formed and destroyed in a given time, since both are products of two different factors — a balance between production and decomposition. Thus an increase in the number of red blood-cells may mean either that more are being formed or less are being broken up — we cannot tell which. Obviously, we must seek to determine separately the quantity formed and the amount destroyed.

We have no way of directly estimating even approximately the number of red blood-cells or the amounts of hemoglobin which are produced. We can only assume, when young forms of red blood-cells are found, that the bone-marrow is probably active and that the formation of red cells is proceeding at a greater rate than usual.

But we are beginning to get a little insight into one part of the other side of the problem, i. e., the rate of destruction of hemoglobin. We know that the quantity of bilirubin formed is directly dependent on the amount of hemoglobin which is decomposed, and we find that when an excess of bilirubin is excreted a larger amount of urobilin and urobilinogen appears in the stools and vice versa. The proportion of urobilinogen absorbed from the intestine introduces a variable factor, but in spite of this the urobilinogen and urobilin content of the stools gives us a reliable indication of the amount of hemoglobin destruction.

As yet we have not had an opportunity to study more than a few cases of anemia by this method, but the results seem to indicate that there is a reciprocal relation between the destruction and formation of hemoglobin, so that when there is a large amount of urobilinogen and urobilin in the stools, evidences of increased rapidity of production are found, while on the other hand in those cases in which the anemia is due to a deficient formation of hemoglobin, the stool examinations show a decrease below the normal in the urobilinogen and urobilin content, as if the body were endeavoring to bring about a return to the normal by slowing the rate of blood destruction.



This point will be best illustrated by citing three cases in which the hemoglobin percentage was less than normal from three different causes: In Case 1 from increased hemoglobin destruction, in Case 2 from decreased hemoglobin formation because of loss of pyrrol nuclei from the body, and in Case 3 from defective formation because of failure of the hemoglobin-producing function of the liver.

In the following table the normal averages as well as those obtained in these cases are given. The figures for urobilinogen refer to spectroscopic dilution values obtained under the same conditions.

	Red Blood Cells	Blood-----		Urobilinogen	
		Hemoglobin Per Cent.	Color Index	Avg. Daily Excretion Stools	Urine
Normal ...	5,000,000	100	1.00	6,475	0
Case 1.....	1,600,000	34	1.07	24,977	470
Case 2.....	2,375,000	28	0.58	2,400	0
Case 3.....	4,100,000	65	0.79	2,095	580

Patient 1 had pernicious anemia. The figures given above are an average of daily observations for twenty-four days. This time may be subdivided into two periods of fifteen and of nine days, respectively.

	Red Blood Cells	Blood-----		Urobilinogen	
		Hemoglobin Per Cent.	Color Index	Avg. Daily Excretion Stools	Urine
Period 1...	1,430,000	31-32	1.10	26,276	604
Period 2...	1,800,000	37-38	1.04	9,546	199

During the first period the rate of hemoglobin destruction as judged from the excretion of urobilinogen and urobilin in the stools, was more than four times as great as normal. Throughout this period normoblasts and megaloblasts were present in considerable numbers.

During the second period the rate of hemoglobin destruction was only moderately increased. No normoblasts or megaloblasts were found in the smears.

Apparently, therefore, when blood destruction was proceeding rapidly, the rate of blood formation was also increased. That it, however, did not succeed in fully compensating for the increased loss is suggested by the lower hemoglobin percentage and red blood-cell count during this period.

In this case in spite of the marked anemia the corpuscles contained slightly more than the normal quantity of hemoglobin. The reason is not far to seek. There was no failure of hemoglobin-forming power, and the liver was supplied with such an excess of urobilin-complex, that part escaped past it into the general circulation. This, then, is an example of a decrease in hemoglobin percentage due to a preponderance of destruction over formation.

Case 2 was an example of anemia from long continued small losses of blood from internal hemorrhoids. The rate of hemoglobin destruction here was much slower than normal. No evidence of rapid blood regeneration was found. In this case each red blood-cell contained only about half as much hemoglobin as the normal. The production of hemoglobin had lagged behind that of the red blood-cell stromata. Yet there was nothing in the case to support the idea that the hemoglobin-forming power of the liver was failing — no advanced anatomical lesion of the liver, no general infection to cause diffuse liver cell degeneration. That this function was, in fact, intact was shown by the fact that the anemia disappeared after a Whitehead operation had been performed, and the loss of blood had been stopped. Why then, since there was less than the normal amount of blood destruction going on within the body, and since the liver function was potentially, at least, unimpaired, was there any anemia at all? Why did not the body compensate at once for the small losses of blood?

The reason is to be found in the distinction which must be drawn between destruction of hemoglobin within the body, and loss of hemoglobin from the body. In Case 1, although the hemoglobin was destroyed, a considerable part of the urobilinogen into which it was disintegrated was reabsorbed as urobilin-complex and supplied the liver with material for the building of new hemoglobin, whereas when blood is lost from the body as in Case 2 the pyrrol nuclei it contains have gone for good and all. There is no possibility of saving any. If such losses are repeated frequently, even though individually they are small, an impoverishment of the body in pyrrol nuclei may ultimately arise, and even though the liver is fully efficient, hemoglobin formation will fail for lack of building material. Even in those cases in which the loss of blood from the body has not been so great as to lead to a decisive decrease in the pyrrol nuclei available for hemoglobin formation, there may be a relative diminution in the amount of hemoglobin which is produced. For the most powerful stimulus to hemoglobin formation would seem to be the product of hemoglobin disintegration — urobilin-complex. Possibly this substance has some specific excitatory influence on the liver cells apart from its use as raw material in the manufacture of hemoglobin.

Case 3 was in a patient with marked cachexia in whom large, irregular abdominal masses were palpable. An exploratory incision revealed general carcinomatosis.

In this case urobilinogen was found in excess in the urine. There was no increased hemoglobin destruction to account for it as in Case 1; in fact, the rate of hemoglobin disintegration was shown by the stool estimations to be much less than normal. A defect in the capacity to

utilize urobilin-complex because of liver degeneration arising from the poisons which had produced the cachectic state found in the patient, was assumed. As in Case 2, each red blood-cell contained less than its usual quota of hemoglobin. The type of anemia was the same in both cases. They were only to be distinguished so far as the study of the blood and excreta went, by the fact that urobilinogen was present in the urine of the patient in Case 3, and absent in that of the patient in Case 2. But this difference is important, for it points to a difference in causation. The decreased hemoglobin production which was common to both cases was produced in Case 2 by pyrrol starvation, whereas in Case 3 it was derived from an inability on the part of the liver to make use of the pyrrol nuclei with which it was supplied.

The success which has attended the introduction of methods of functional diagnosis in connection with the kidneys, stomach, pancreas, etc., has stimulated many efforts to find a satisfactory test for the liver also.

The functional efficiency of the kidneys can be estimated by the study of the amount and rate of excretion of water, nitrogen, chlorids and phenolsulphonephthalein. By means of the stomach-tube and the Roentgen rays we can arrive at conclusions as to the secretory and motor power of the stomach. Test diets and stool examinations reveal any marked abnormality in the absorptive capacity of the intestine, or in the secretion of the pancreas. But we have no well established and widely used test of liver function. We still have to depend in the diagnosis of most hepatic disorders on anatomical changes which are frequently absent, and on symptoms which are often misleading.

A consideration of the methods of functional diagnosis, which have proved useful in other organs, would indicate that the basis of any hepatic test must be some work performed by the liver alone. Now the liver has many functions, but what are the specific functions peculiar to the liver?

Ten, or even five years ago, the list of such probably exclusive functions was longer and there was less doubt and hesitation about most of them than there is now. Yet it is within these years that great efforts have been made to answer this question. Workers in many different fields have joined in a general attack on the problem from all sides. Clinical pathology has acted as a sort of skirmishing force in the front of this attack, and has often temporarily occupied positions which later have had to be abandoned, as the accumulation of well established knowledge has shown them to be untenable. History, especially recent history, is full of this, and a review of the work of the last decade shows that the advance has been, in the main, a retreat and a retrenchment.

Thus, we used to hold that the synthesis of urea from ammonia, water and carbon dioxid could be carried out only by the liver, but now we know that urea may be produced elsewhere. The more recently advanced test of liver function based on the capacity of the liver to remove ammonia from amino-acids has also been shown, by the fine work of Van Slyke and Meyer<sup>17</sup> and others, to rest on an insecure foundation.

The knowledge that creatin appears in the urine in conditions of disturbed carbohydrate metabolism, and not only in cases in which liver function is particularly disorganized, has thrown doubt on the hypothesis that the transformation of creatin into creatinin is a special function of the liver alone. The work of Fischler<sup>18</sup> with Eck-fistula dogs has shown that Strauss' contention that levulose can be converted into glycogen only by the liver has no foundation in fact, at least as regards warm-blooded animals.

The capacity of the liver to form sugar from certain amino-acids, which may be one of its specific functions, cannot be utilized as a test of liver efficiency except in phloridzinized dogs or the severest forms of diabetes.

The tests founded on the so-called detoxicating functions of the liver have not proved clinically useful and Rothberger and Wintersberg<sup>19</sup> have come to the conclusion that there is no sufficient evidence that the liver has any capacity in this respect which other tissues do not also possess.

In general, it seems that the hopes that have been entertained of finding some distinctive and necessary part played by the liver in the chemical reactions involved in the intermediary protein, fat and carbohydrate metabolism of the tissues, on which to found a functional test, do not at present seem likely to be fulfilled.

The more we learn about the intermediary metabolism of the tissues, the more does it seem that these processes are too generalized to form a basis for testing the function of any one organ.

But there is a group of chemical changes in the body which to a great extent may be regarded as shut off from the general tissue metabolism, namely, the processes concerned with the formation, decomposition, and excretion of the substances which go to form the blood.

It is sometimes said that the blood is a tissue, as much a tissue as muscle or connective tissue. The analogy may be correct in many particulars, but it remains true that the blood is widely separated both

17. Van Slyke and Meyer: *Jour. Biol. Chem.*, 1913-1914, xvi, 213.

18. Fischler: *Verhandl. Cong. f. inn. Med.*, Wiesbaden, 1913.

19. Rothberger and Wintersberg: *Arch. Pharmacod.*, 1905, xv, 339.

in its physical characters and in its functions from any other tissue of the body; and this separation of the blood becomes clearer the more we learn about the chemical changes involved in its metabolism.

Thus the other tissues grow from within themselves by assimilating and incorporating substances abstracted from the blood. But the essential components of the blood are not built within itself, but are given to it ready formed from the other tissues, exactly the reverse process.

The products of the breaking down of the other tissues — urea, uric acid, creatinin, etc. — are removed from them and carried by the blood to the kidneys for excretion, but many, at least, of the special and peculiar end-products of the components of the blood itself are eliminated not through the kidneys, but through the liver.

It is just because of this very separation of the blood metabolism from general tissue metabolism that it is possible to recognize defects in the hemoglobin-forming capacity of the liver. It is this distinction that makes urobilinogen estimations a valuable and practical test of hepatic function. But here the excretion of urobilinogen in the urine alone is not decisive, for a large increase over the usual amount may be determined by augmented hemoglobin destruction quite apart from any liver disturbance. Only when the hemoglobin disintegration has been shown by quantitative estimations of urobilinogen and urobilin in the stools to be within or below the normal limits, does urobilinogenuria acquire any significance as an indication of liver insufficiency.

It may be found that the hypothesis which has been advanced as to the rôle played by the liver in the metabolism of hemoglobin pigment is applicable in some degree to other constituents of the blood. It is significant that the bile acids, taurocholic and glycocholic acid, are most readily accounted for as derivatives of the decomposition of the red blood-cell stromata and that they follow the urobilinogen in its absorption from the intestine and its passage to the liver. The part played by the liver in the formation of fibrinogen has long been known, and it is possible that the serum albumin, serum globulin and the protein constituent of hemoglobin have the same origin.

These are interesting possibilities, but it must be admitted that the data as yet are too meager to allow of any constructive theorizing. It is facts rather that are needed.

It is otherwise with hemoglobin pigment metabolism. Here we have a mass of chemical, experimental and clinical findings which have never been satisfactorily coordinated. In particular, I believe that in urobilinogenuria we have a valuable method of recognizing hepatic disturbances which has been misused and misinterpreted since the time of Jaffé, because the relations between this phenomenon and hemoglobin formation and destruction have never been formulated.

Finally, and this is a point of great importance, if this hypothesis is well founded, we have in urobilinogen and urobilin estimations in the excreta a method which will give us valuable information in the investigation into the cause of various types of anemia.

#### SUMMARY

The hemoglobin liberated from outworn red blood-corpuscles is separated into pigment and protein. Within the liver cells the pigment is converted into bilirubin. In the large intestine bilirubin is reduced to urobilinogen.

The change from hemoglobin pigment to urobilinogen is accomplished by intramolecular rearrangements. The four pyrrol nuclei retain their characteristic grouping. Only the side chains are altered.

But in the form of urobilinogen the pigment molecules have acquired two new properties. They have become diffusible, so that they can be absorbed into the portal blood-stream, and they have a tendency to take up oxygen and become linked in pairs, a process of oxidative polymerization which results in the formation of the body known as urobilin.

In the formation of hemoglobin the urobilinogen absorbed from the intestine, since it retains the essential structure of the blood pigment, would form a readily available building material. A difficulty in accepting this as a possibility lies in the fact that urobilinogen has never been found within the body. But here the capacity for polymerization under the influence of oxygen which urobilinogen possesses suggests the reason. The first product of this reaction — urobilin — disappears into some unknown substance, under the same conditions which favor its own formation from urobilinogen. This is assumed to be a continuation of the same process of polymerization, so that a body is formed which consists of an unknown number of urobilinogen molecules linked together. This hypothetical substance has been termed urobilin-complex. It is in this form that urobilinogen exists in the blood and in the tissues.

The kidneys decompose urobilin-complex into urobilinogen. But under normal conditions, although urobilinogen is constantly being absorbed and converted into urobilin-complex in the portal blood-stream, there is practically no urobilinogen in the urine because the urobilin-complex is removed by the liver.

The data we possess on the varying capacity of the liver to absorb and hold urobilin-complex under various experimental and clinical conditions cannot be explained on the assumption that the liver simply stores up the urobilin-complex, but they are in accordance with the conception that the liver has some active work to perform in connection



with this substance. It is maintained that this work consists in the restitution of the original side chains to the pyrrol nuclei of the urobilinogen molecule, so that hemoglobin pigment is formed again from its own decomposition product.

The surest indication of the presence and of the degree of a generalized disturbance of the liver function is based on the determination of the extent of failure of this synthesis of hemoglobin pigment from urobilin-complex.

There is another and more complicated synthesis of hemoglobin pigment from those pyrrol nuclei which are not, as in urobilinogen, prearranged in their proper relationships to one another. For there is a daily loss of pyrrol nuclei from the body in the stools, and the urobilinogen which is absorbed from the intestine cannot replace the total amount of hemoglobin pigment which is constantly being disintegrated. But of this synthesis, of the site, and of the manner of its building, we, as yet, know nothing.

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# A REPORT OF THE BACTERIOLOGICAL EXAMINATION OF ENLARGED LYMPH-NODES REMOVED FROM A PATIENT WITH HODGKIN'S DISEASE\*

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The question of the etiological basis of that type of lymph-node hypertrophy referred to as Hodgkin's disease, has for many years been of much interest. There have been two principal ideas in regard to this type of lymph-node hyperplasia; one that it is a neoplasm of the lymphoblastic elements of the lymph-nodes, the other that it is an inflammatory reaction accompanying or following an infection with some micro-organism which attacks especially the lymph-nodes.

The advocates of each of these theories have referred to the histological findings in the lymph-nodes as evidence in support of one or the other of the two theories referred to above. Among others, Gibbons,<sup>1</sup> has expressed the opinion that the enlarged nodes belong in the group of malignant neoplasms. Opposed to this view are McCallum, Longcope, Reed and others who have claimed that the histological findings in the lymph-nodes are those associated with a chronic inflammatory irritant of some kind. Professor Adami in his recent text-book expresses the belief that the lymph-node lesions in Hodgkin's disease are not those of a true neoplasm, but are of a chronic inflammatory nature.

There have appeared in the comparatively recent literature reports that deal with the demonstration of micro-organisms in the nodes themselves. Fränkel and Mutch have reported the results of their study of the enlarged lymph-nodes from a number of cases of "Hodgkin's disease." These authors were able to demonstrate in twelve out of thirteen cases the presence of micro-organisms in the excised lymph-nodes. These organisms were demonstrated in the material remaining after treating the tissues with antiformin. From the morphological and staining characters of the organisms found they were of the opinion that they were either a type of tubercle bacillus or that they belong to a type closely related to the tubercle bacillus.

The infectious basis of Hodgkin's disease has not been limited to the microscopical demonstration of organisms in the lymph-nodes. Negre and Meerimet report the isolation of an organism from the

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\* From the Pathological Laboratory of the Montreal General Hospital.

1. Gibbons: *Am. Jour. Med. Sc.*, 1906, cxxxii, 692.

enlarged lymph-nodes removed from two patients with Hodgkin's disease. These organisms were recovered by the use of special medium. Their article gives a description of the organism isolated. The most recent work dealing with the etiology of this disease has been done by Bunting and Yates<sup>2</sup> and reported recently. In their first paper they report the results obtained from the bacteriological study of a series of enlarged lymph-nodes removed from patients whose clinical picture corresponded to that found in Hodgkin's disease, and whose lymph-nodes themselves showed the histological picture found in this disease. The general summary of the work on which this paper is based is as follows: From three out of five cases of Hodgkin's disease, in which a bacteriological examination had been made, a pure culture of a diphtheroid, pleomorphic organism has been isolated in pure culture. In the remaining two cases this organism was recognized, but not recovered in pure culture. The morphology, cultural and staining reactions of the organism recovered from one patient is briefly as follows:

They are facultative anaerobes, Gram-positive, not acid fast, and vary greatly in their morphology depending on a number of factors, e. g., their age, the medium employed and the fluid content of the medium. Pleomorphism is a pronounced feature, coccoid forms, long forms, beaded forms, club-shaped involution forms, are present. Branching forms are present especially on the egg medium. On certain media polar staining forms are present. Plate cultures show rounded, glistening, gray colonies which at the end of twenty-four hours gradually become opaque white. There is a central dark spot in the colony and a fine stippling of the growth.

Since the publication of the above article these same investigators have reported<sup>3</sup> the results thus far obtained by inoculating animals with the diphtheroid organism they have isolated.

They have been able by repeated inoculations not only to infect monkeys (*Macacus rhesus*), but these animals have shown a blood-picture typical of that of early Hodgkin's disease and later have developed chronic lymphadenitis that corresponds grossly and microscopically with Hodgkin's disease in man, of the same duration. Not only have they succeeded in producing these gross and histological changes in the monkey, but they have recovered from the enlarged lymph-nodes a diphtheroid organism similar in every way to the organisms injected. In one of their articles they say:

Thus, since our experiments demonstrate that the diphtheria organism is pathogenic for monkeys, that it produces a progressive enlargement of the lymph-nodes, with lesions similar to those of Hodgkin's disease in man, and further that the blood changes in the monkey are similar to those in man, we feel fully assured of the etiologic relationship of the diphtheroid organism (*Bacterium hodgkini*) to Hodgkin's disease.

2. Bunting and Yates: Culture Results in Hodgkin's Disease, THE ARCHIVES INT. MED., 1913, xii, 236.

3. Bunting and Yates: Jour. Am. Med. Assn., 1913, lxi, 1803.

We have recently had the opportunity of making a bacteriological study of the enlarged lymph-nodes from a patient with Hodgkin's disease. This opportunity was made possible through the kindness of Dr. J. M. Elder, on whose service the patient was admitted to the Montreal General Hospital. The clinical history is briefly as follows:

*History.*—The patient is a white woman, aged 21. The present illness began two years ago, in 1912, with swelling in the right side of the neck. The swelling increased slowly and did not produce discomfort. In 1913, one year after the first symptoms were noted, a swelling appeared in the left side of the neck. About this time she had a normal pregnancy, after which she became gradually weaker, feverish and easily tired. On exertion she had dyspnea and palpitation of the heart. No pain was present. Patient thinks she lost about fifteen pounds in weight.

Patient has been married five years and has had two children (both died in infancy). She has always been well previous to present illness. There is no family history of tuberculosis.

*Examination of Glandular System.*—At the base of the neck there are two large masses on either side of the middle line. These masses are about 7 cm. in diameter. The skin is freely movable over them. The masses themselves are movable on the underlying tissues and on palpation are found to be made up of discrete individual masses varying in size from 1.5 to 4 cm. in diameter. The smaller growths have a distinctly elastic feel. There is one slightly enlarged lymph-node in the right axilla; otherwise the axillae are free. Below the right clavicle the superficial veins of the thorax are dilated and tortuous. This finding was interpreted as evidence of pressure on the mediastinal vessels. A roentgenogram shows a definite shadow in the mediastinum which corresponds to an area of dulness noted on percussion.

The edge of the spleen is just palpable. On percussion splenic dulness is 16 by 9 cm.

Blood examination shows the following:

White cells .....	14,200
Red blood-cells .....	2,440,000
Hemoglobin .....	60 per cent.

Differential blood-count is as follows:

Polymorphonuclear leukocytes .....	50 per cent.
Small mononuclears .....	31 per cent.
Large mononuclears .....	9 per cent.
Eosinophils .....	9 per cent.
Mast cells .....	1 per cent.
Blood-pressure.....	Systolic, 100; diastolic, 80

On January 26, 1914, Dr. Elder removed, under local anesthesia, three enlarged lymph-nodes from the left side of the neck. This operation was done with the greatest of aseptic precautions. The three nodes were at once taken to the laboratory for examination. Under careful aseptic precautions a portion of each node was taken for bacteriological investigation, and at the same time sections of the nodes were put into fixing solutions for histological study.

*Pathological Report.*—M. G. H., S-14-58. The specimen consists of three discrete, encapsulated lymph-nodes. They measure 2 cm., 25 cm. and 4 cm. in diameter, respectively. The nodes are loosely united by delicate fibrous tissue. Each node is enclosed in its own capsule and is only loosely united with those about it. The tissues immediately surrounding the lymph-nodes are edematous and contain numerous small blood-vessels. The nodes are only a little firmer than normal. On section they are of a uniform pale, grayish-white color, with a slight yellowish cast. The incised surfaces show a semitranslucent appearance. The following microscopical description is based on Zenker and formalin fixed tissues, sections from which have been stained with eosin and methylene blue, hematoxylin and eosin, Mallory's phosphotungstic acid, hematoxylin, and connective-tissue stain. Specimens from each node have been examined for bacteria both by means of direct smears made from the nodes and by means of staining sections for bacteria. Histologically the sections of the lymph-nodes show briefly the following: The pericapsular tissues are edematous and show a slight cellular infiltration. The infiltrating cells are for the most part lymphocytes. The capsules of the nodes are slightly thickened and infiltrated with lymphocytes. The lymph-node parenchyma has largely lost its normal histological characters. There are no germinal centers. There is a moderate, though not extensive, increase in connective tissue. This connective tissue increase is more marked in certain places. The most striking cellular change is the increase in endothelial leukocytes and the presence of large multinucleated cells. These multinucleated cells occur irregularly distributed throughout the section. There are but few eosinophils found. No necrotic areas or areas of acute inflammatory change are found.

In the direct smears from the nodes there are a few Gram-positive bacilli with morphology similar to the organisms recovered by means of culture. The organisms are few in number. Many fields are examined before one is found. None of them are intracellular. In sections from the nodes stained by Gram-Weigert's method and a modified Gram-Weigert's there are only a very few bacilli demonstrated. These organisms have always appeared as single organisms, they lie free in the tissue spaces and the cellular characters of the tissue immediately surrounding them is in no way different to that elsewhere in the nodes. A careful search for organisms within the cells, especially within the multinucleated cells, has been made. In no instances have we been able to find intracellular organisms.

The bacteriological procedure consisted in excising small bits of each of the lymph-nodes. Some of these were thoroughly macerated in warm sterile saline solution. Other pieces of tissue were inoculated directly in various mediums, the tissue first being thoroughly rubbed over the surface of the medium. The finely macerated tissue was inoculated in large and small amounts on various mediums. Both aerobic and anaerobic cultures were made and incubated at 37.5 C. The inoculated media were examined from time to time. At the end of eighteen hours one tube of human blood agar showed a growth of Gram-positive cocci in groups. None of the other mediums showed positive results until ten days after their inoculation, when a stained smear from one of the hydrocele agar tubes showed Gram-positive organisms. The organisms were mostly of the coccoid and cocco-bacillary type, though a few bacilli were present. Within the next two weeks, twenty-one days after their original inoculation, a number of the tubes showed organisms on stained smears. The presence of colonies on the original tubes could be definitely made out only on certain mediums. Growth was first recognized in the gross by a finely stippled-like appearance to the surface of the medium. The colonies were largest on the hydrocele agar. On this medium they developed near the water of condensation as small, almost transparent colonies. The surface of Dorset egg medium showed a fine stippled appearance. There slowly developed a grayish precipitate in bouillon, and in the water of condensation of the solid medium, especially where the water of condensation was abundant. In two of the tubes of hydrocele

agar, where large amounts of hydrocele had been added, a grayish cloudy growth developed at the bottom of the tube and gradually spread outward between the agar and the inner surface of the culture tube. In the original tubes of solid medium, growth was most abundant in those which contained large amounts of fluid. The presence of the pleomorphism of the organisms found in our original culture led us to the strong suspicion, at one time, that we were dealing with at least two different organisms. But by transplanting all colonies that showed few bacilli and many coccoid and coccobacillary forms on proper mediums, especially Dorset egg medium, bacillary forms predominated especially in the younger cultures.

A series of transplants has been made on various mediums and the organisms grown through several generations. The morphological characters of these organisms have varied greatly on different mediums, and under varying growth conditions. Cultures of the same age on various mediums show certain characters common to them all and certain characters that vary in the different mediums. They are all Gram-positive and non-motile and none of them is acid fast. The resistance to acid decolorization has been studied by using Gabbet's method and the Ziehl-Neelson method of staining for tubercle bacilli. In using the Ziehl-Neelson method varying dilutions of acids have been employed as decolorizing agents, and the results obtained compared with a young culture of tubercle bacilli (human type), *Bacillus typhosus* and *Staphylococcus pyogenes aureus*. These organisms were smeared on the same slide, and, in so far as possible, smears were made of uniform thickness. In the staining process each slide has been treated similarly. The following results have been obtained: Dilutions of nitric acid for decolorizing were employed from 30 per cent. strength down to 0.5 per cent. The organisms under consideration, *Bacillus typhosus* and *Staphylococcus aureus* were completely decolorized in all of the dilutions used, while the tubercle bacillus remained acid fast throughout.

The morphological characters of the organism in Dorset egg medium is as follows: Most of the organisms are of a definite bacillary type. Many of them show sharp, deeply staining granules within them. These granules may be either unipolar, bipolar, or bipolar with two or more deeply staining areas in the bodies of the organisms between the two poles. The form of the bacillus is not constant. Most of them are comparatively long and narrow and show varying degrees of curving. There are a few branching forms with or without polar bodies in them. As many as four branches have been found in one organism.

A series of roll cultures were made using agar with various percentages of fluid medium, as hydrocele, defibrinated blood, etc.

A series of these tubes was inoculated under both anaerobic and aerobic conditions. In all the roll cultures growth developed, but the most luxuriant growth took place in the anaerobic cultures, especially in those containing proportionately large amounts of fluid. In both the anaerobic and aerobic cultures colonies did not appear at all or only sparsely and slowly within the first 1 to 1.5 cm. of the upper surface of the medium. At this point there developed a narrow band of closely packed colonies. This band varied in width: in some of the tubes it reached 3 cm. in others it was only a few millimeters. Below this point the colonies were not nearly as numerous though they were present throughout the remainder of the mediums. There slowly developed a heavy grayish diffuse growth between the outer surface of the medium and the inner surface of the culture tubes. This growth was most marked in the lower half of the tube.

The organism as a rule has not grown in fluid medium as well as in the solid medium.



## SUMMARY

We have isolated from the enlarged lymph-nodes of a patient who showed the clinical picture of Hodgkin's disease, and from whom excised glands histologically corresponded to this disease, a pure culture of a pleomorphic, Gram-positive, non-motile, non-acid fast, facultative anaerobic organism, similar to those described by Bunting and Yates.

Cultures of the organism isolated by us have been repeatedly injected into the tissues about the axillae of an adult monkey (*Macacus rhesus*), but up to the time of this report we have obtained no conclusive results.

# THE OCCURRENCE OF MALIGNANT NEOPLASMS IN THE YOUNG

AS SHOWN BY AN ANALYSIS OF 2,000 CASES OF MALIGNANT NEOPLASMS  
EXAMINED IN THE PATHOLOGICAL LABORATORY OF  
THE UNIVERSITY OF MICHIGAN \*

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The present study is based on an analysis of 2,000 cases of malignant neoplasm contained in a total of 3,600 cases of neoplasm examined microscopically in the Pathological Laboratory of the University of Michigan during the years 1895-1913. This material is the same as that used in the two papers by Dr. Weller and myself<sup>1</sup> in *THE ARCHIVES OF INTERNAL MEDICINE* in 1913. As stated there, the material studied is a homogeneous one, derived almost entirely from the state of Michigan, and representing the average population of the state. Further, the material has been utilized not only for the purposes of practical diagnosis, but also in the teaching of pathologic histology, so that the percentage of error in diagnosis can be safely regarded as reduced to a minimum. This point is of especial importance, since the majority of statements concerning the occurrence of malignant neoplasm in the young are to be found in writings of the Virchow period when no exact differentiation of carcinoma and sarcoma was made, and when malignant teratoid tumors were classed as sarcoma or carcinoma or chondroma, etc., as the case might be, according to the preponderance of one or the other of the elements making up the growth. Doubt is, therefore, justly thrown on many of the diagnoses in the reported cases of congenital and early-life tumors. As Williams has mentioned, this is particularly true of the tumors described as "epitheliomata."

The age-period of 1 to 30 years has been chosen, as covering the entire period of development. It is of the greatest importance as far as the broad general neoplasm problem is concerned to establish the relations existing, if any, between the origin of neoplasms and the

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\* Read before the Association of American Pathologists and Bacteriologists, Washington, D. C., 1913.

\* From the Pathological Laboratory of the University of Michigan, Ann Arbor, Mich.

1. Weller, C. V.: Age Incidence in Carcinoma, *THE ARCHIVES INT. MED.*, 1913, xii, 539. Warthin, A. S.: Heredity with Reference to Carcinoma, etc., *ibid.*, p. 546.

periods of bodily growth. The statement is frequently met in the literature that the development of malignant neoplasms is especially related to the climacterics. It is essential to know if such a relationship exists in the case of the lesser climacterics as well as of the grand. In the consideration of the occurrence of neoplasms in the young the first three decenniums should be taken as covering the periods of dentition, puberty, youth and early sexual maturity, if this question is to be settled. This has not yet been done. The greater number of the reports of malignant neoplasm has been concerned almost wholly with the question of *earlyness*. Numerous cases of congenital and early-life neoplasms are recorded in the transactions of pathologic societies with reference to this one point; but little analysis has been made of collected cases from the more important point of view.

Of the 2,000 cases of malignant neoplasms studied, 195, or 9.75 per cent., occurred in the age-period 1 to 30 years. Of these 108 cases, or 55.4 per cent., were in males, and 87, or 44.6 per cent., in females (Table 1). The forms of neoplasms and their distribution through the thirty years is as follows:

## AGE INCIDENCE

FIRST YEAR	SEVENTH YEAR
Rhabdomyosarcoma of kidney.	Osteochondrosarcoma of femur.
Round-cell sarcoma of orbit.	EIGHTH YEAR
Lymphosarcoma of intestines.	Spindle-cell sarcoma of orbit.
Adenosarcoma of kidney, congenital.	Large round-cell sarcoma of tibia.
Malignant teratoma of testis.	NINTH YEAR
Angiosarcoma of eye.	Large round-cell sarcoma of leg.
Myosarcoma of femur.	Fibrosarcoma of nose.
Congenital fibrosarcoma of neck.	TENTH YEAR
Round-cell sarcoma of eye.	Osteosarcoma of foot.
Spindle-cell sarcoma of jaw.	Spindle-cell sarcoma of eyelid.
Adenorhabdomyosarcoma of kidney.	Round-cell sarcoma of tibia.
	Small round-cell sarcoma of orbit.
SECOND YEAR	ELEVENTH YEAR
Lymphosarcomatosis.	Squamous-celled carcinoma of leg.
Angiosarcoma of eye.	Sarcoma of eye.
	Lymphosarcoma of intestine.
THIRD YEAR	TWELFTH YEAR
Small spindle-cell sarcoma of radius.	No cases.
Rhabdomyosarcoma of kidney.	THIRTEENTH YEAR
Spindle-cell fibrosarcoma of neck.	No cases.
Lymphosarcoma of orbit.	FOURTEENTH YEAR
FOURTH YEAR	Spindle-cell sarcoma of ulna.
Lymphosarcoma.	Squamous-cell carcinoma of mouth.
Myosarcoma of bladder.	Carcinoma of stomach.
Squamous-celled carcinoma of ear.	Osteosarcoma of pelvis.
Rhabdomyosarcoma of testis.	Adenocarcinoma of umbilicus (con-
Small round-cell sarcoma of eye.	genital).
FIFTH YEAR	Basal-celled carcinoma of eye.
No cases.	
SIXTH YEAR	
Lymphosarcomatosis.	
Round-cell sarcoma of femur.	

## AGE INCIDENCE—(CONTINUED)

## FIFTEENTH YEAR

Adenocarcinoma of ovary.  
Endothelioma of orbit.

## SIXTEENTH YEAR

Osteochondrosarcoma of femur.  
Alveolar sarcoma of tibia.  
Large round-cell sarcoma of uterus.  
Medullary carcinoma of ovary.  
Large spindle-cell sarcoma of clavicle.  
Osteosarcoma of tibia.  
Osteochondroma of scapula.  
Round-cell sarcoma of femur.

## SEVENTEENTH YEAR

Spindle-cell sarcoma of tibia.  
Sarcoma of parotid region.  
Osteosarcoma of femur.

## EIGHTEENTH YEAR

Basal-cell carcinoma of eye.  
Malignant teratoma of ovary.  
Osteosarcoma of humerus.  
Colloid carcinoma of colon.  
Round-cell sarcoma of skin of thigh.

## NINETEENTH YEAR

Malignant teratoma of ovary.  
Small round-cell sarcoma of orbit.  
Alveolar round-cell sarcoma of ribs.  
Large spindle-cell sarcoma of brain.  
Spindle-cell sarcoma of bladder.  
Metastatic carcinoma in cervical lymph-nodes.  
Squamous-celled carcinoma of cheek.  
Melanotic sarcoma of skin.

## TWENTIETH YEAR

Colloid carcinoma of intestine.  
Spindle-cell sarcoma of parotid.  
Malignant syncytioma of uterus.  
Malignant teratoma of testis.  
Scirrhus carcinoma of stomach.  
Fibrosarcoma of jaw.  
Small spindle-cell sarcoma of jaw.  
Spindle-cell sarcoma of face.  
Fibrosarcoma of popliteal space.

## TWENTY-FIRST YEAR

Squamous-celled carcinoma of cervix.  
Myosarcoma of femur.  
Basal-celled carcinoma of conjunctiva.  
Lymphosarcomatosis.  
Giant-cell sarcoma of ulna.

## TWENTY-SECOND YEAR

Squamous-celled carcinoma of skin of abdomen.  
Osteosarcoma of pubis.  
Giant-cell sarcoma of jaw.  
Lymphosarcomatosis.  
Squamous-celled carcinoma of eye.  
Small round-cell sarcoma of fibula.

## TWENTY-THIRD YEAR

Squamous-cell carcinoma of skin.  
Carcinoma of breast.  
Lymphosarcomatosis.  
Basal-cell carcinoma of eye.  
Colloid carcinoma of cecum.

## TWENTY-FOURTH YEAR

Adenocarcinoma of cecum.  
Adenocarcinoma of breast.  
Adenocarcinoma of ovary.  
Osteochondrosarcoma of pelvis.  
Alveolar round-cell sarcoma of neck.  
Malignant teratoma of testis.  
Fibrosarcoma of nose.  
Malignant teratoma of testis.

## TWENTY-FIFTH YEAR

Squamous-cell carcinoma of chin.  
Medullary carcinoma of breast.  
Malignant teratoma of testis.  
Osteosarcoma of femur.  
Lupus-carcinoma of face.  
Lupus-carcinoma of cheek.  
Melanotic sarcoma of skin.  
Giant-cell sarcoma of jaw.  
Myosarcoma of uterus.  
Malignant teratoma of testis.

## TWENTY-SIXTH YEAR

Sarcoma of skin.  
Basal-cell carcinoma of lip.  
Round-cell alveolar sarcoma of humerus.  
Squamous-celled carcinoma of cervix.  
Spindle-cell fibrosarcoma of jaw.  
Fibrosarcoma of breast.

## TWENTY-SEVENTH YEAR

Adenocarcinoma of uterus.  
Carcinoma of antrum.  
Spindle-cell sarcoma of breast.  
Lymphosarcomatosis.  
Medullary squamous celled carcinoma of cervix.  
Squamous-celled carcinoma of lip.  
Adenocarcinoma of uterus.  
Squamous-celled carcinoma of hand.  
Malignant teratoma of testis.  
Adenocarcinoma of thyroid.  
Squamous-celled carcinoma of cervix.

## TWENTY-EIGHTH YEAR

Malignant teratoma of testis.  
Cystocarcinoma of ovary.  
Carcinoma of breast.  
Squamous-celled carcinoma of lip.  
Rodent ulcer of eye.  
Scirrhus carcinoma of pylorus.  
Malignant teratoma of testis.  
Medullary round-cell sarcoma of popliteal space.  
Sarcoma of ovary.

## AGE INCIDENCE—(CONTINUED)

## TWENTY-EIGHTH YEAR—(Continued)

Endothelioma of neck.	Medullary carcinoma of cervix.
Malignant teratoma of testis.	Endothelioma of chin.
Squamous-celled carcinoma of mouth.	Squamous-cell carcinoma of cervix.
Cystadenocarcinoma of breast.	Myosarcoma of cervix.
Squamous-celled carcinoma of lip.	Lymphosarcoma.
	Cystocarcinoma of ovary.
	Myosarcoma of uterus.

## TWENTY-NINTH YEAR

Spindle-cell sarcoma of femur.	Squamous-cell carcinoma of penis.
Carcinoma of parotid.	Medullary carcinoma of breast.
Cystocarcinoma of ovary.	Carcinoma of breast.
Endothelioma of orbit.	Medullary carcinoma of cervix.
Squamous-celled carcinoma of penis.	Medullary carcinoma of breast.
Adenocarcinoma of tube.	Lymphosarcomatosis.
Rodent ulcer of inner canthus.	Squamous-celled carcinoma of cervix.
Endothelioma of mouth.	Medullary carcinoma of cervix.
Squamous-celled carcinoma of cervix.	Adenocarcinoma of rectum.
Adenocarcinoma of rectum.	Adenosarcoma of cervix, congenital.
Squamous-celled carcinoma of cervix.	Malignant syncytioma of uterus.
Basal-celled carcinoma of lip.	Lymphosarcomatosis.
Medullary carcinoma of breast.	Squamous-celled carcinoma of cervix.
Basal-celled carcinoma of nose.	Medullary carcinoma of breast.
Squamous-celled carcinoma of lip.	Scirrhus carcinoma of breast.
	Squamous-celled carcinoma of lip.
	Cylindroma of parotid.
	Squamous-celled carcinoma of leg.
	Squamous-celled carcinoma of lip.
	Myosarcoma of uterus.

## THIRTIETH YEAR

Spindle-cell sarcoma of ovary.
Melanotic sarcoma of skin.
Spindle-cell sarcoma of heel.

The types of neoplasms were divided as follows: carcinoma 77, or 39.5 per cent.; sarcoma 92, or 47.3 per cent.; malignant teratoma 19, or 9.7 per cent.; malignant syncytioma 2, or 1 per cent.; endothelioma 5, or 2.5 per cent. If the malignant syncytioma and the malignant teratoma be added to the carcinoma, as all of the latter showed atypical epithelial proliferations, even in many cases to the extent of producing epithelial metastases of the nature of carcinoma, and as malignant syncytioma is epithelial in origin, it will be seen that the types of malignant neoplasms in this series are nearly evenly divided between connective-tissue and epithelial growths (Table 1).

TABLE 1.—MALIGNANT NEOPLASMS, 2,000 CASES; IN THE AGE PERIOD 1-30 YEARS, 195 CASES, OR 9.75 PER CENT.

	Cases	Per Cent.
Males .....	108	55.4
Females .....	87	44.6
Carcinoma .....	77	39.5
Sarcoma .....	92	47.3
Malignant Teratoma .....	19	9.7
Malignant Syncytioma .....	2	1.0
Endothelioma .....	5	2.5

Of the carcinomas the distribution as to locality was as follows: antrum 1, breast 12, eye and conjunctiva 7, small intestine 1, colon 1, cecum 2, rectum 2, lip 9, lymph-nodes 1, mouth 2, ovary 6, parotid 1, penis 2, tube 1, hand 1, leg 2, ear 1, cheek 2, nose 2, chin 1, elbow 1, stomach 2, pylorus 1, umbilicus 1, cervix of uterus 12, endometrium 2, thyroid 1 (Table 2).

TABLE 2.—SITE OF CARCINOMA

Antrum .....	1	Skin, back of hand .....	1
Breast .....	12	Leg .....	2
Eye, conjunctiva .....	7	Ear .....	1
Intestine .....	1	Cheek .....	2
Colon .....	1	Nose .....	2
Cecum .....	2	Chin .....	1
Rectum .....	2	Elbow .....	1
Lip .....	9	Stomach .....	2
Lymph-Nodes, metastatic .....	1	Pylorus .....	1
Mouth .....	2	Umbilicus .....	1
Ovary .....	6	Uterus, cervix .....	12
Parotid .....	1	Endometrium .....	2
Penis .....	2	Thyroid .....	1
Tube .....	1		

The distribution of the sarcomas with respect to site was: bladder 2, jaw 7, femur 10, tibia 6, fibula 1, heel 1, foot 1, pelvis 3, humerus 2, ulna 2, radius 1, rib 1, scapula 1, clavicle 1, brain 1, breast 2, eye 5, eyelid 1, orbit 5, face 1, intestine 2, lymph-nodes 10, muscle of abdomen 2, neck 4, nose 2, ovary 2, parotid 3, popliteal space 2, skin 5, body of uterus 4, cervix 2 (Table 3).

TABLE 3.—SITE OF SARCOMA

Bladder .....	2	Breast .....	2
Bone and Periosteum—		Eye .....	5
Jaw .....	7	Eyelid .....	1
Femur .....	10	Orbit .....	5
Tibia .....	6	Face .....	1
Fibula .....	1	Intestine .....	2
Heel .....	1	Lymph-nodes .....	10
Foot .....	1	Muscle, abdominal .....	2
Pelvis .....	3	Neck .....	4
Humerus .....	2	Nose .....	2
Ulna .....	2	Ovary .....	2
Radius .....	1	Parotid .....	3
Rib .....	1	Popliteal space .....	2
Scapula .....	1	Skin .....	5
Clavicle .....	1	Uterus .....	4
Brain .....	1	Cervix .....	2

The distribution of the malignant teratomas was: cervix of uterus 1, kidney 4, ovary 2, testis 12. The endotheliomas were distributed as follows: chin 1, orbit 2, mouth 1, neck 1 (Table 4).

TABLE 4

SITE OF MALIGNANT TERATOMA		SITE OF ENDOTHELIOMA	
Cervix uteri .....	1	Chin .....	1
Kidney .....	4	Orbit .....	2
Ovary .....	2	Mouth .....	1
Testis .....	12	Neck .....	1

The chart shows graphically the age distribution. It will be seen by this that the curve is high during the first year, falls then to rise at puberty, after which there is a steady rise up to the limit of the



period, age 30. The large number in the first year emphasizes the importance of the *congenital factor*, and this influence is felt in the case of the majority of the tumors found up to the period of sexual ripeness, even when no actual evidences of a teratoid nature could be demonstrated in the tumor. Sarcoma predominates in the period of infancy and childhood; but the *parallel increase of both sarcoma and carcinoma with age is noteworthy and in contradiction to the usual belief that sarcoma is essentially a disease of childhood*. The cases of malignant teratoma fall in the periods of early childhood and developing sexual life. Particularly is this the case with the malignant tera-

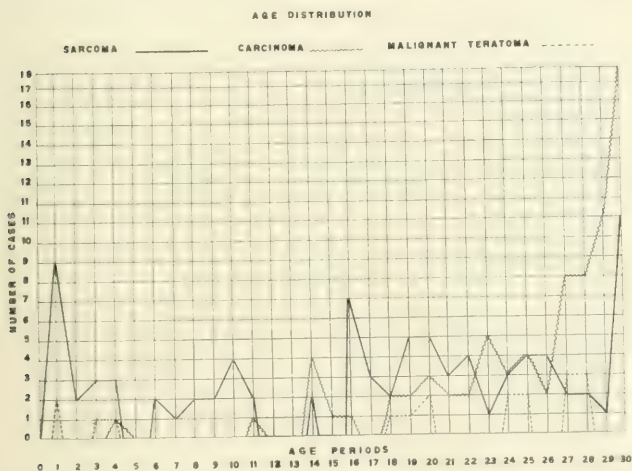


Chart showing age distribution of sarcoma, carcinoma and malignant teratoma.

tomas of testis and ovary, the majority of these cases developing after puberty and in the early period of sexual maturity. No especial relationship to the period of dentition is shown. We had no cases in the fifth year, and none in the twelfth and thirteenth years. The number of cases in the years 6 to 11 is too small to show any conclusion. The main facts shown by the chart are the relatively high number of congenital tumors, the gradual increase in incidence of tumors from the age of adolescence into mature life, the relation of malignant teratomas to puberty and the parallel incidence of carcinoma and sarcoma.

The best analysis of congenital and early-life neoplasms is that by Williams.<sup>2</sup> The analysis of our 195 cases of malignant neoplasms of this period differs in a number of ways from his. His analysis is based on Duzan's analysis of 182 malignant tumors of early infancy, Picot's analysis of 424 cases, his own of 56 consecutive cases, Poinso's 25 cases of bone sarcoma in infancy, Gross' study of sarcoma of the long bones (51 cases) and 41 cases tabulated by Butlin and Colby. Williams points out the relative frequency of retinal glioma and renal tumors as congenital. No retinal glioma occurs in my series, and only four cases of congenital neoplasm of the kidney. Likewise the tendency to sarcoma observed by him on the part of the scapula is not shown in our series, only one case being included.

Williams concludes that prenatal life, infancy and childhood are wholly exempt from malignant epithelial tumors. He rejects many of the reported cases as untrustworthy. He gives the earliest age at which carcinoma has been positively demonstrated as 11 years (columnar-celled cancer of rectum). He himself saw a case of rodent ulcer at 14 years. He asserts that under the age of puberty cancer is practically unknown. In our list we find an undoubted and typical squamous-celled horny cancer of the lobe of the ear at 4 years (no evidence of teratoid origin could be found); at 11 years a typical horny squamous-celled carcinoma of the skin of the leg; in the fourteenth year an adenocarcinoma of the umbilicus (teratoid in origin), a typical squamous-celled carcinoma of the mouth, a basal-celled carcinoma of the eye and an adenocarcinoma of the stomach. Our list then gives undoubted examples of earlier carcinoma than those recorded by Williams. He also reports the earliest examples of cancer of the breast as occurring at 20.5 and 21 years. Our list gives two operated on in the twenty-third year, the tumors having begun to develop before the twentieth year.

My conclusions in the main agree with those of Williams. Malignant tumors are relatively rare before puberty, but there is a steady ascending line of occurrence from childhood onward to middle life, *both sarcoma and carcinoma showing a parallelism of occurrence*. This fact is also strikingly brought out in the study of sarcoma by Dr. Weller. Our cases in a large measure also support Williams' view of the *congenital or teratoid origin of malignant neoplasms in infancy and early life*.

*The tendency to malignant tumors is relatively slight before sexual maturity is reached, increases during the period of sexual maturity, up to the age-period of 58 to 62. With the decline of the organism the tendency to malignant neoplasm decreases.*

## EXPERIMENTAL DIABETES INSIPIDUS IN DOGS\*

S. A. MATTHEWS

LAWRENCE, KAN.

It is a well substantiated clinical observation that injuries involving the base of the cranium frequently are followed by polyuria which may or may not be accompanied by glycosuria. It is also just as well substantiated that growths which involve the base of the brain, especially the region of the third ventricle, may likewise give rise to polyuria which may be accompanied by hyperglycemia sufficient to produce glycosuria. These conditions when arising from fractures of the base of the skull generally are of short duration, but when they result from growths in the region above mentioned, may be more or less persistent.

The first experimental evidence that injuries to the base of the brain (in the region of the fourth ventricle) gave rise (under certain conditions of the animal operated on) to polyuria accompanied by hyperglycemia and glycosuria was furnished by the classic experiment of Bernard known as the Bernard piqûre. Further, it has been observed that certain piqûres in the base of the brain may give rise to polyuria alone without glycosuria. As Bernard failed to induce any glycosuria by his piqûre after section of the splanchnic nerves, or in fasting animals, our present-day interpretation of his results would be that he was dealing with an epinephrin glycosuria. However that may be, Cushing<sup>1</sup> and his coworkers have thrown some doubt on this interpretation, as well as on the assumption of the existence of a diabetic center in the floor of the fourth ventricle, and have brought forward much experimental evidence to show that the glycosuria induced by the Bernard piqûre is in all probability of hypophyseal origin. The same evidence is applicable to the polyuria induced by piqûres further forward in the brain.<sup>2</sup>

All workers in this field have noted that the injection of extracts of the posterior lobe cause a rise in the blood-pressure generally accompanied by a transient (more lasting than the increase in blood-pressure) polyuria. Like observations<sup>3</sup> on the volume of the kidneys

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1. Cushing, H.: *Bull. Johns Hopkins Hosp.*, 1913, xxiv, 40.

2. Cushing, by stimulating certain nerves of the autonomic system (Langley) which make connection with the pituitary body, and which he claims controls its secretion, was able to bring about these conditions (polyuria and glycosuria), which he explains in terms of hypersecretion of the nervous part of the gland.

3. King and Stoland: *Am. Jour. Physiol.*, 1913, xxxii, 405.

show the following general results: Immediately following the beginning of the rise in blood-pressure there is a contraction of the kidneys, during which time the secretion of the urine is almost suspended. Following this initial contraction and anuria the kidneys begin to dilate and often attain a degree of dilatation much above the normal. Accompanying and during the time the kidneys remain dilated (about thirty minutes from a single dose) there is a marked polyuria, sometimes glycosuria. The intensity of the diuresis induced is always proportional to the degree of kidney dilatation and only lasts as long as the kidneys remain dilated. This is paramount to saying that the diuretic effect of posterior lobe extracts is due to a local dilatation of the kidney vessels, thus allowing a greater quantity of blood to pass through the kidneys per unit of time than under normal conditions, just as the diuresis induced by caffeine or strophanthus can be accounted for in terms of kidney volume.

Nearly all the investigations so far on the function of the pituitary body have brought out the fact that certain injuries of the posterior lobe or of the stalk, such as partial removal of the lobe or irritation of the stalk, frequently are followed by polyuria; sometimes, though less frequently, by glycosuria, generally transient but sometimes persisting for weeks, in which case the polyuria is accompanied by a great laying-on of fat.<sup>4</sup> In two young female dogs I was able to induce a permanent polyuria (a veritable diabetes insipidus) accompanied by a rapid accumulation of fat by operating on the base of the brain as follows:

A hole about 5 mm. in diameter was drilled with an ordinary dental burr, driven by a dental engine, from the roof of the mouth up through the sphenoid bone into the floor of the sella turcica. The opening removed the posterior rim of the pituitary fossa and extended back about 5 mm. This exposed the posterior surface of the posterior lobe and the region just posterior to it. The hole in the sphenoid bone was then plugged with a gutta-percha compound such as is used for temporary fillings in teeth. The plug was placed so that it would impinge somewhat on the posterior lobe and its stalk and extend up into the third ventricle.

Both animals recovered from the effects of the operation, and the wounds healed without infection. No nasal trouble followed. No sugar was found in the urine secreted during the time of the operation, nor at any subsequent time. Only a small amount of urine was passed (about 150 c.c.) during the forty-eight hours following the operations. After the second day polyuria began to develop. One of these animals in particular (weight 6 kg.) after the fourth day required from 5 to 6 liters of water every twenty-four hours to make it comfortable and passed from 5 to 6.5 liters of urine per day for nine weeks, and in the same time gained three kilos in weight. While the animal was not eating, drinking and urinating, it simply slept and grew fat. With an abundance of water (6 to 7 liters) the amount of urine voided per twenty-four hours was about equal to the amount of water imbibed; but if water was given more sparingly (4 liters) the tendency was to pass more urine than the

4. Cushing, H.: Boston Med. and Surg. Jour., 1913, clxviii, 901.

water imbibed. If given an ordinary amount of water (300 to 500 c.c.) about 600 to 800 c.c. urine would be passed, and the animal would show signs of distress. The dog enjoyed a good appetite throughout, eating well of table scraps, etc. The sugar tolerance was high; in fact it was impossible to induce an alimentary glycosuria, the animal being able to ingest 15 gm. of glucose per kilo body weight in six hours without showing any signs of glycosuria.

The urine passed was simply a dilute normal urine (specific gravity 1.001-1.002). The amount of nitrogen eliminated when computed in terms of the food eaten and a normal amount of urine (250 to 300 c.c.) was about normal. Also the relative amounts of the different nitrogen constituents of the urine were normal. In fact, there was no change in the nitrogen metabolism. The inorganic salts were approximately normal. With a given amount of water, sufficient to maintain physical comfort (6 liters), the concentration of the urine remained about constant (specific gravity 1.001-1.002). With less water the urine tended to become more concentrated. Ordinary quantities of water, less than 2 liters per day, caused great physical discomfort.

During the animal's life after the operation (nine weeks) it gained 3 kilos (50 per cent.) which seemed to be almost wholly represented by an accumulation of fat. While it was found impossible to induce an alimentary glycosuria, the animal responded promptly to phlorizin with a copious output of sugar.<sup>5</sup>

The dog's temperature remained low throughout, not more than 37 C., and the state of lethargy in which it remained indicated profound hypopituitarism as defined by Cushing.

*Necropsy.*—The hole in the sphenoid bone included about 1 mm. of the posterior part of the pituitary fossa and extended posteriorly about 4 mm. The plug of temporary dental stopping had healed into the bone and protruded up along the posterior surface of the gland for about 4 mm. It had impinged somewhat on the nervous portion of the gland and the point of the plug was in close proximity to the stalk at its entrance into the floor of the third ventricle. The plug had exerted considerable pressure on the posterior lobe and the stalk, but not sufficient to destroy the gland, nor materially to change its structure. The anterior lobe was apparently normal and the base of the brain was perfectly clean.

Outside of the cranium the principal pathological finding was an excessive accumulation of fat, not only in the regions of the body where fat normally deposits, but all the tissues were infiltrated with fat. It was noticed before death that the heart was not working well; and when opened deposits of fat were found on the valves and in the interstices of the papillary muscles sufficient to occupy a large part of the space in the heart's cavities. In fact, all the spaces and interstices in the muscles of the body everywhere were distended with fat. The muscle cells themselves were not well nourished. All the glandular organs were infiltrated with fat, and the liver especially showed numerous necrotic areas. The kidneys were small and the cells contained an excess of fat. The glomeruli were full of fat. No marked inflammatory changes had occurred in the tubular epithelium, although the cells did not stain well.

Cushing and his coadjutors as well as nearly all other workers in this field have described the occurrence of intense polyurias, generally of short duration, following the partial removal of the nervous lobe of

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5. An attempt was made to inhibit the formation of fat in these dogs by keeping them under the influence of phlorizin, but abscesses tended to form at the site of the injections, so this had to be discontinued. In fact, both animals had to be sacrificed on account of abscess formation due to hypodermic medication.



the gland and also after insult to the stalk. Some of the animals described exhibited a moderate polyuria lasting for months, accompanied with an abnormal accumulation of fat.

There is sufficient evidence now at hand to establish beyond doubt that certain manipulations of the posterior lobe, such as partial removal or injuries to the stalk, will induce a temporary polyuria and that continuous irritation of a small degree, such as slight pressure, may bring on a permanent polyuria (diabetes insipidus). Cushing<sup>4</sup> evidently brought on this condition in one patient by a sellar decompression operation, in which only a small fragment of anterior lobe tissue was removed. In dogs, experimental diabetes insipidus is accompanied by marked symptoms of hypopituitarism and an accumulation of fat. From the clinical reports at hand, this rapid accumulation is not so apparent, although nearly all the other signs of hypopituitarism have been described.<sup>6</sup>

To form a true picture from the experimental data at hand of the mechanism which operates to induce polyuria and polydipsia is quite impossible. One might imagine that by certain manipulations of the gland, such as has been described and which are followed by polyuria and polydipsia, the posterior lobe can be thrown into a state of hypersecretion; and that the excess of the secretion acts in the same manner as the injection of posterior lobe extract. This would give rise to a general vasomotor contraction of short duration followed by a local vasomotor dilatation of the kidney vessels of a more lasting character. Such a change in the relative blood-supply between the body as a whole and the kidneys always gives rise to diuresis. In fact, all chemical compounds possessed of diuretic properties act on the vascular system in this way (caffein; strophanthus; pituitrin). Should one attempt to explain the polyuria and polydipsia arising from hypophyseal derangements, such as has been described in terms of the diuresis caused by the injection of extracts of the posterior lobe, the following explanation (more or less transcendental) seems to satisfy at least a number of the observed facts:

To conform with this generally accepted interpretation of the action of extracts of the posterior lobe in causing diuresis, the kidneys will have to be looked on as dialyzing membranes and the urine as a dialysate. This conception makes the dialyzing membranes (kidneys) permeable to all the normal constituents of the urine, and the rate of dialysis to depend on the concentration in the blood of the constituents of the urine, and the amount of the solution of these substances (blood) which comes in contact with the dialyzing membranes per unit

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6. Marie and Boutier: *Rev. neurol.*, 1913, xxv, 555.



of time. Such a mechanism as this would tend to deplete the body of water as well as of the effete materials given off from the tissues into the blood, the solution of which in water constitutes the urine.<sup>7</sup>

Ordinarily, the circulation through the kidneys is about sufficient to permit of the passage of about 1,500 c.c. of water with its contained substances (urine) per day. To maintain life and comfort this water must be replenished from the outside, which is accomplished by absorption from the stomach and intestines. When a certain amount of water has passed from the body a disagreeable sensation begins to manifest itself in the mouth and the pharynx, which is relieved by the imbibition of water. When water passes rapidly through the kidneys or is given off from the surface of the body in large amounts, this sensation occurs at frequent intervals, and if the excretion of water is very rapid, it may be almost continuous (polydipsia). This is analogous to the sensation referable to the stomach called hunger. When the tissues begin to suffer from lack of food, some influence begins to exert itself on the stomach, causing contractions which give rise to painful sensations called hunger pains, and which are relieved by the taking of food. In diabetes mellitus the body cannot utilize one of the chief food substances (carbohydrates) and in extreme cases hunger pains are almost constant.<sup>8</sup> Likewise when the kidneys permit the passage of an excessive amount of water, polydipsia results.

As already stated, diuresis results whenever an excess of blood is permitted to pass through the kidneys in a given time, as compared with the blood passing through the remainder of the body in the same time. This deviation from the normal relation of the kidney blood-supply to the tissues in general would tend to draw off the water from the body to an extent sufficient to cause polydipsia. Should the kidneys attain to a great degree of dilatation, such as often occurs after the injection of pituitrin, the elimination of water might be sufficiently rapid to cause a constant state of polydipsia, and if one were allowed to imagine a condition of prolonged dilatation of the kidneys to result, a state of polyuria and polydipsia comparable to the dog described might well result.

While this explanation satisfies quite well most of the conditions present in the polyurias and polydipsias of hypophyseal origin, both clinical and experimental, it can hardly be said that there is sufficient

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7. Water and the inorganic salts are essential to life and must therefore be considered as foods. If the effete materials which result from cell metabolism appear in the urine as dialysates they must first be held in a state of solution. So it would appear that one of the functions of water in the animal economy is that of a solvent for these effete substances, and that its excretion is necessary to accomplish their excretion.

8. Luckhardt: *Am. Jour. Physiol.*, 1914, xxxiii, 313.

experimental evidence at hand to support it unconditionally, although experimental evidence in its support is not wholly wanting. We can hardly say, however, that we have sufficient evidence at hand to prove that operations on the pituitary body such as are followed by polyuria and polydipsia, or that such pathological lesions as give rise to polyuria, cause a hypersecretion of the posterior lobe of the gland sufficient to keep the kidneys in a dilated state for weeks or months. Neither have we sufficient evidence to claim that a constant hypersecretion of the posterior lobe will keep the kidneys in a state of dilatation, nor do we know that repeated doses of posterior lobe extract over a long time will accomplish any such results. In fact, Farini,<sup>9</sup> P. Bioch,<sup>10</sup> R. Balnet<sup>11</sup> and von den Velden<sup>12</sup> claim that in human subjects the injection of posterior lobe extracts exerts no diuretic influence at all, and that when administered to patients suffering from diabetes insipidus they reduce the amount of urine passed to or below normal. In normal dogs injections of posterior lobe extract twice daily failed to modify the amount of urine passed over a period of seven days.

Direct stimulation of the posterior lobe or of the nerves going to it generally cause a contraction of the kidneys which may last for a few minutes only (ten to fifteen) to be followed by a dilatation accompanied by diuresis, or the initial contraction may last for hours (twenty-four to forty-eight) eventually to be followed by polyuria, which argues for a dilatation of the kidneys. Frequently, while drilling through the sphenoid bone in pituitary operations, an oncometer record of the kidney volume being taken at the same time, I have observed a contraction of the kidney which sometimes continued throughout the operation with almost complete suppression of the urine. In fact, anuria may continue for forty-eight hours after the operation. Under like conditions I have noted an initial contraction of the kidney to be followed in from ten to fifteen minutes by dilatation and diuresis, and at other times and under identical conditions a dilatation of the kidneys from the first accompanied by diuresis.

While these observations seem contradictory, nevertheless, when scrutinized, their lack of agreement is more apparent than real. The experimental evidence seems to bring out quite clearly that continued stimulation (irritation) not of sufficient intensity to destroy the integrity of the gland, may give rise to a state of polyuria and polydipsia of long duration, lasting at least as long as the stimulation lasts, provided, however, the integrity of the gland is preserved. Operations,

9. Farini: *Riforma med.*, 1913.

10. Bioch, P.: *München. med. Wehnschr.*, 1914, Ixi, 217.

11. Balnet, R.: *Berl. klin. Wehnschr.*, 1913, I, 2379.

12. von den Velden: *Berl. klin. Wehnschr.*, 1913, I, 2085.

such as direct stimulation of the gland for a short time only, or partial or total removal of the gland, induce a diuresis of short duration, and if we admit that the diuresis results from a setting free of an excess of the gland's secretion, as long as the effects of the excess secretion lasts. As to whether in these cases of experimental diabetes insipidus the volume of the kidneys is increased, we have no direct evidence. In fact, we have no method at hand to demonstrate whether or not such a condition exists.<sup>13</sup>

As for the explanation of the excessive formation of fat under these conditions, none is at hand. Carbohydrates seem to be rapidly converted into fat, which may account for the high sugar tolerance of the animals. At any rate it seems that the food value of the carbohydrates is reduced very much under the conditions imposed, and that the real condition of the body at the end is that of emaciation. In diabetes mellitus the body cannot use the sugars, so in experimental diabetes insipidus of pituitary origin in dogs the body does not seem to be able to utilize either the sugars or the fats to their full extent.

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13. The theory that in diabetes insipidus some substance is liberated in the body that renders the kidney epithelium permeable only to dilute solutions, could not be made to hold in these dogs. The kidneys here were permeable to a urine, having a specific gravity of 1.010, as shown by the imbibition of salt and limiting the water supply.

# THE USE OF STRYCHNIN AND CAFFEIN AS CARDIO-VASCULAR STIMULANTS IN THE ACUTE INFECTIOUS DISEASES \*

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For decades many physicians have relied, with unquestioning faith, on strychnin in the treatment of certain grave symptoms occurring in pneumonia, typhoid fever and other acute infectious diseases. Within the last twenty-five years some physicians have preferred to use caffein (and other drugs) when confronted with these symptoms. The symptoms referred to are those which are thought to signify an approaching or an already existing failure of the circulation, and strychnin and caffein are often believed to be powerful and rapid stimulants for the cardiovascular apparatus in such a state.

It is the object of this communication to discuss briefly the question whether failure of either the heart or the vasomotor apparatus is the chief cause of death in the infectious diseases; and to examine, with the aid of new data, the pharmacological and clinical evidence for and against the use of strychnin and caffein as cardiovascular stimulants in infections.

## THE ALLEGED FAILURE OF THE CIRCULATION

A normal flow of blood is brought about chiefly by two factors — a heart which pumps a sufficient amount of blood, and a peripheral resistance maintained by the partial contraction of the small arteries. The tone of the arteries depends, in its turn, on the normal activity of the vasomotor nervous system.

*The Heart.*—It is one of the axioms of clinical medicine that the heart-muscle may be so seriously damaged in the acute infections as to be an important source of death. The symptoms which are alleged to signify approaching heart failure of this type are rapid pulse, irregular pulse, dyspnea, cyanosis, increased area of cardiac dulness and weak heart sounds. Space does not permit a discussion of each one of these symptoms. Occasion will, however, be taken to point out

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that at least the cyanosis<sup>1</sup> and dyspnea<sup>2</sup> may not be of cardiac origin; that an increased area of dulness is a rare finding in this connection, and that most clinicians have great difficulty in judging of the relative strength of heart-sounds.

Nor is the experimental evidence more satisfying. In 1899, Romberg, Pässler, Bruhns and Müller<sup>3</sup> investigated, by means of experiments on animals, the cause for the cardiovascular disturbances of the acute infectious diseases. They produced a fatal pneumococcus septicemia, fatal diphtheria, and a fatal pyocyanous infection in rabbits. Even when the animals were near death, upward stroking of the abdomen still caused a moderate rise in blood-pressure, and clamping the abdominal aorta was still followed by a sharp rise in pressure. Romberg and his coworkers argued that if the heart-muscle were exhausted, it would yield before an increasing load, and so the two above-mentioned maneuvers would not result in a rise of blood-pressure. Stejskal<sup>4</sup> disagreed with their conclusions because he was able to show that abdominal massage could increase arterial pressure even in a dead animal. Gottlieb<sup>5</sup> also felt that Romberg's data did not justify his conclusions. MacCallum<sup>6</sup> has recently reinvestigated the state of the heart in fatal diphtheria intoxication. He says in one place:

There is no comparison between the perfused normal heart and the diphtheria hearts, all of which are feeble and apt to go into fibrillation. Nevertheless, although one may receive the impression that the hearts from the poisoned animals are rather weak and apt to be irregular, it is clear that they continue to beat for several hours after they have shown every sign of failure in the body of the dying animal, if only the pressure of nutritive fluid be maintained in the coronary arteries. Indeed, the animal may be allowed to die, and an hour after its death the heart can be revived and will beat for a long time. All of this seems to show fairly well that the death which occurs in the height of an attack of diphtheria is not exclusively the result of direct injury to the heart, although that may play some part in the process.

Such are the data concerning the state of the myocardium in the acute infectious diseases. It is difficult to draw conclusions from them. Certain symptoms, such as rapid and irregular pulse, and dyspnea

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1. Peabody, F. W.: The Oxygen Content of the Blood in Lobar Pneumonia. *Jour. Exper. Med.*, 1913, xviii, 7.

2. Barcroft, J.: The Respiratory Function of the Blood, 1914, Camb. Univ. Press.

3. Romberg, Pässler, Bruhns and Müller: Exp. Untersuchungen über die allg. Path. der Kreislaufstörung bei acuten Infectiouskrankheiten, *Arch. f. klin. Med.*, 1899, lxiv, 652.

4. Stejskal, K. R.: Kritisch. Exp. Untersuchungen über den Herztod in Folge von Diphtherietoxin, *Ztschr. f. klin. Med.*, 1902, xlv, 367.

5. Gottlieb: *Med. Klin.*, 1905, p. 25.

6. MacCallum, W. G.: The Mechanism of the Circulatory Failure in Diphtheria. *Am. Jour. Med. Sc.*, 1914, cxlvii, 37.

occurring in the course of acute infections, may logically be offered as evidence that the heart is seriously threatened. On the other hand, the data collected from experiments on animals fail to show that the heart-muscle is exhausted by these diseases. But these latter data are not entirely satisfactory, because, being negative, they are open to the criticism that a new method of attack might bring forth positive evidence of serious myocardial injury.

*The Peripheral Resistance.*—Having proved to their satisfaction that the heart could not be directly responsible for the disturbances in question, Romberg and his associates presented further data which they interpreted to mean that the vasomotor apparatus was paralyzed in these diseases. Clinicians accepted this hypothesis and quickly began to direct their therapeutic efforts against this new agent of death. A new reason now existed for the use of strychnin and caffein in these diseases, because both of these drugs were said to be powerful vasomotor stimulants.

But it has been recently shown that the vasomotor apparatus does not fail in pneumonia or diphtheria. Porter and Pratt<sup>7</sup> and Porter and Newburgh<sup>8</sup> have found the vasomotor reflexes normal in all stages of diphtheria and pneumonia; and Newburgh and Minot<sup>9</sup> have shown that the blood-pressure is usually not low in fatal pneumonia. If the vasomotor apparatus is normal in pneumonia and diphtheria, it may be assumed that it also maintains its integrity in other acute infections. Such an assumption is, at least, justified until evidence against it is presented.

To sum up this portion of the discussion, it may be stated (1) that since there is no evidence that the vasomotor apparatus is injured in the acute infectious diseases, it is not logical to direct treatment chiefly toward this apparatus; (2) that the hypothesis that the heart may be fatally injured in the acute infections, although far from proved, is still tenable in the present state of our knowledge, and that it is consequently logical to attempt to assist it when it seems to be failing.

We turn now to strychnin and caffein, two of the drugs so frequently used as cardiovascular stimulants.

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7. Porter and Pratt: The State of the Vasomotor Center in Diphtheria Intoxication, *Am. Jour. Physiol.*, 1914, xxxiii, 431.

8. Porter and Newburgh: The State of the Vasomotor Apparatus in Pneumonia, *Am. Jour. Physiol.*, 1914, xxxv, No. 1.

9. Newburgh and Minot: The Blood-Pressure in Pneumonia, *THE ARCHIVES INT. MED.*, 1914, xiv, 48.



## STRYCHNIN

Strychnin is used in the treatment of the acute infectious diseases because it is believed that it raises the blood-pressure, slows the pulse and increases the force of the heart. But a search through the literature shows that there is not a single piece of experimental evidence to warrant such a belief.

In fact, Mayer<sup>10</sup> in 1871 and Denys<sup>11</sup> in 1885 showed that strychnin in medicinal doses did not change the blood-pressure or the rate of the heart beat. They studied the effect of increasing doses of strychnin on the pressure in the carotid artery of animals and found that the pressure did not rise until the dose was sufficiently great to cause convulsive twitchings, which began simultaneously with the upward movement of the pressure curve. It is important to note that Mayer and Denys worked with non-curarized animals, for results obtained in animals which have been given enough curare to abolish the reflex muscular contractions leave no means of determining whether an amount of strychnin sufficient to raise blood-pressure is not also great enough to cause convulsions. One is not justified in concluding that because strychnin, if given in sufficiently great doses, has a pressor effect in curarized animals, it will have the same effect when given to human beings in medicinal doses.

When the use of strychnin in myocardial disturbances is impartially investigated, it is found that the evidence all points in one direction. Pharmacologists<sup>12</sup> have shown that strychnin is without effect on the heart until given in doses so large that death from convulsions invariably ensues. Clinicians<sup>13</sup> have demonstrated that strychnin is of no benefit in the treatment of acute or chronic heart disease.

There are two clinical studies of the effect of strychnin in the acute infectious diseases.

Cook and Briggs<sup>14</sup> in 1903, recorded the effects of stimulants in hypotensive states. In summing up their results with strychnin they said in part:

Strychnin produces a rise in blood-pressure varying in average cases from one to four hours, and accompanied, in the majority of patients carefully observed, by an improvement in the patient's general condition. When the

10. Mayer, S.: *Ber. d. kais. Acad. d. Wissensch.*, 1871, lxiv, 657.

11. Denys, J.: *Arch. f. exper. Path. u. Pharmacol.*, 1885, xx, 306.

12. Ingersheimer, J.: *Ueber die Wirkung des Strychnines auf das Kalt- und Warmblüterherz.*, *Arch. f. Exper. Path. u. Pharmacol.*, 1905, liv, 73.

13. Parkinson and Rowlands: *Strychnin in Heart Failure*, *Quart. Jour. Med.* 1913, vii, 42. Newburgh, L. H.: *On the Use of Strychnin in Broken Cardiac Compensation*, *Am. Jour. Med. Sc.*, 1915, cxlix.

14. Cook and Briggs: *Clinical Observations on Blood-Pressure*, *Johns Hopkins Hosp. Rep.*, 1903, xi, 451.

routine administration of strychnin has continued for from eight to twelve doses, individual doses often fail to produce any marked immediate rise in the systolic blood-pressure; but in such cases, if one or two doses are omitted and the pressure is carefully followed in the interval, it will be seen that there is a progressive fall in blood-pressure in the absence of stimulation, the previous level being again restored when the drug is renewed. On the whole, strychnin is by far the most satisfying cardiovascular stimulant for long continued routine administration.

Such results should have been easy of confirmation. Cabot<sup>15</sup> undertook this task the next year. His observations include five thousand measurements in thirty-one cases of typhoid fever, four of pneumonia and fifteen others. The total result was negative. He was unable to convince himself that strychnin exerts any influence on the blood-pressure in febrile cases. Cabot's experience was such as an acquaintance with the pharmacology of the drug would lead one to expect. I shall present data which are in entire accord with those collected by Cabot.

This review of the studies of the action of strychnin must make it evident that there is no reason for prescribing it as an aid to a failing myocardium. Cook and Briggs' enthusiastic recommendation of it as a powerful pressor agent is not supported by laboratory data and is directly refuted by Cabot's investigations.

#### CAFFEIN

Caffein has also been credited with the ability to stimulate the vasomotor mechanism and to increase the effectiveness of the heart beat. When we examine the evidence on which the use of caffein as a vasomotor stimulant ought to be based, we find that there has been constant disagreement among experimenters. Some have asserted that caffein had a powerful pressor effect through its action on the vasomotor center. Others have stoutly denied this. In a recent review of the whole subject the reasons for the confusion have been pointed out and new data have been added which finally place the action of caffein on the cardiovascular apparatus on a firm basis.<sup>16</sup> This work presents the following summary:

The circulatory effects of moderate doses of caffein consist in vasodilatation combined with sufficient cardiac stimulation to maintain or even increase blood-pressure. Both of these activities favor blood flow. The oncometer shows conclusively that the moderate rise of pressure which is observed in anesthetized animals is, in most cases, exclusively cardiac.

15. Cabot, R. C.: Measurements of Blood-Pressure in Fevers, Before, During and After Administration of Strychnin, *Trans. Assn. Am. Phys.*, 1904, xix, 22.

16. Sollmann and Pilcher: The Actions of Caffein on the Mammalian Circulation, *Jour. Pharm. and Exper. Therap.*, 1911, iii, 19.

Caffein then does not stimulate the vasomotor center, but it does augment the circulation in the way described above, at least in experimental animals whose hearts were presumably normal. Whether it has a similar beneficial effect in diseased hearts remains still to be demonstrated.

#### NEW OBSERVATIONS OF THE EFFECTS OF STRYCHNIN AND CAFFEIN

*Method.*—We have collected clinical data in regard to the question whether strychnin and caffein are valuable cardiovascular stimulants. The observations were made on patients in all stages of acute infectious diseases and in a few others who exhibited very low blood-pressure.

The effect of single doses of varying size, or a number of doses given within a short period of time, on the systolic, diastolic, and pulse-pressure, on the rate and character of the pulse, and the respiratory rate, and on the general condition, was studied. It has been our invariable procedure to measure the blood-pressure, to count the pulse, and usually the respiration, several times immediately before giving the drug and every few minutes thereafter, until it was certain that either no effect had been produced or that the effect had come to an end. Repeatedly, such measurements were made two or more times daily throughout the period of illness, so that the drug period could be compared over several days with the period preceding it and the period following it.

*Limitations of the Method.*—When judging of the effect of any therapeutic procedure on the blood-pressure, one must thoroughly realize that moderate and even large variations result from slight external stimuli of all sorts. For example, Zabel,<sup>17</sup> who investigated the causes for sudden changes in pressure, found that a superficial pin prick caused a systolic rise of 72 mm. in one individual and that the average rise following this stimulus lay between 11 and 30 mm. External cold always caused a rise. Even the application of the unheated cuff of the blood-pressure apparatus caused a variation of 23 mm. in one case. The sight of food produced a considerable rise, drowsiness a fall. Psychic stimuli caused variations of from 30 to 46 mm. He found a normal daily afternoon rise. Even if the measurements were carried out under ideal conditions, that is, by the same observer on the same subject, in bed, in a room by himself, on a uniform diet, the temperature of the room being constant, and the subject being in good health and not exposed to any unpleasant sensa-

17. Zabel: Plötzliche Blutdruckschwankungen und ihre Ursachen, München. med. Wchnschr., 1910, lvii, 2278.

TABLE 1.—SHOWING THE EFFECT OF STRYCHNIN IN SINGLE AND REPEATED DOSES ON SYSTOLIC AND DIASTOLIC BLOOD-PRESSURE, PULSE AND RESPIRATION

Type	Case No.	Treatment	Systolic Pressure. Duration of Rise or Fall *	Diastolic Pressure. Duration of Rise or Fall *	Pulse. Duration of Increase or Decrease in Rate *	Respiration. Dura- tion of Increase or Decrease in Rate *
Mild typhoid	10	Strychnin, gr. 1/20 subcutaneously.	↑ 10-13 for thirty minutes.	0	0	Not noted
Same case	10	Strychnin, gr. 1/10 subcutaneously.	↑ 10 for four min- utes	↓ 10 for forty min- utes	0	Not noted
Mild typhoid†	11	Strychnin, gr. 1/10 subcutaneously.	↑ 12-16 for thirty minutes.	↑ 30 for fifteen minutes	0	Not noted
Mild lobar pneumonia	12	Strychnin, gr. 1/10 subcutaneously at 10:15 and 11:15 a. m.	↑ 10 for two hours.	↓ 15 for one and one-half hours.	↓ 10 for remainder of day.	↓ 5 for two hours.
Same case	12	Physical examina- tion next morn- ing.	↑ 20-30 for one hour +	↑ 25 for ?	Not noted	Not noted
Mild lobar pneumonia	13	Strychnin, gr. 1/10 subcutaneously at 12 and 1:30 p. m.	0	0	↑ 5-10 for three hours	0
Mild lobar pneumonia	14	Strychnin, gr. 1/10 subcutaneously at 4 and 5:15 p. m.	↑ 8 for one hour.	0	0	↑ 4 for two hours
Fatal lobar pneumonia	15	Strychnin, gr. 1/10 subcutaneously at 9:20 and 10:05 a. m.	↑ 5-10 for two hours.	0	0	0

Severe lobar pneumonia Same case	16	Strychnin, gr. 1/20 subcutaneously.	0	↑ 5 for one-half hour	0	Not noted
	16	Strychnin, gr. 1/10 subcutaneously.	0	↓ 8 for rest of day	0	Not noted
Fatal pneumonia Injections	17	Strychnin, gr. 1/5 subcutaneously.	0	↑ 10 30 for one hour	↑ 15 for one-fourth hour	Not noted
Colitis	18	Strychnin, gr. 1/10 subcutaneously.	↑ 10 for one-fourth hour.	0	0	Not noted
Same case	18	Sterile H <sub>2</sub> O subcutaneously one hour later.	↑ 10-12 for twenty minutes.	↑ 5 for one hour	0	Not noted
Delirium tremens	19	Strychnin, gr. 6/10 subcutaneously in six hours.	↑ 15 after first injection, then falling to original level.	Could not be accurately read.	↓ 5-8 for two hours	0
Fatal pneumonia	20	Strychnin, gr. 1/10 subcutaneously.	0	0	0	?
Fatal tuberculous colitis	21	Strychnin, gr. 1/10 subcutaneously.	↑ 10 for one-half hour.	Could not be accurately read.	0	0
General peritonitis	22	Strychnin, gr. 1/40 subcutaneously at 9:18 and 10:50 a. m.	0	Could not be accurately read.	0	0
Surgical shock; recovery	23	Strychnin, gr. 1/10 subcutaneously.	0	Could not be accurately read.	0	0
Severe typhoid	24	Strychnin, gr. 1/10 subcutaneously.	0	0	0	0

\* ↑ rise or increase; ↓ fall or decrease.

† The systolic pressure three days later at the same time of day was only 8 mm. less than the greatest height following strychnin, and 20 higher than it had been the previous morning.

TABLE 2.—SHOWING EFFECT OF CAFFEIN SODIO-SALICYLATE IN SINGLE AND REPEATED DOSES ON SYSTOLIC AND DIASTOLIC BLOOD-PRESSURE, PULSE, AND RESPIRATION

Type	Case No.	Treatment	Systolic Pressure. Duration of Rise or Fall *	Diastolic Pressure. Duration of Rise or Fall *	Pulse. Duration of Increase or Decrease in Rate *	Respiration. Dura- tion of Increase or Decrease in Rate *
Fatal lobar pneumonia	15	Caffein, gr. 1½ subcutaneously.	0	0	0	0
Fatal lobar pneumonia	17	Caffein, gr. 1½ subcutaneously each two hours for three days.	0	0	0	0
Fatal lobar pneumonia	20	Caffein, gr. 1½ subcutaneously each two hours for five doses.	↑ 35 during these ten hours	↓ 10 during these ten hours.	↑ 10 during ten hours.	0
General peritonitis	22	Caffein, gr. 5 subcutaneously.	0	Could not be accurately read.	0	0
Fatal tuberculous enteritis	21	Caffein, gr. 5 subcutaneously.	0	Could not be accurately read.	0	0
Traumatic shock	23	Caffein, gr. 5 subcutaneously.	0	Could not be accurately read.	0	0
Same case	23	Scrubbing wound with tinct. iodine.	↑ 20 30 permanently.	?	0	0
Fatal septico-pyemia	25	Caffein, gr. 5 subcutaneously.	0	0	↓ 8 for less than fifteen minutes	0
	25	Caffein, gr. 5 subcutaneously at 10:50, followed by gr. 3 at 11:50, ten days later.	0	0	0	0
Same case	25	Caffein, gr. 17 in eight hours.	Not observed	Not observed	0	0
Surgical shock	26	Caffein, gr. 5, subcutaneously.	0	0	0	0

\* ↑ rise or increase; ↓ fall or decrease.



tions, variations in the readings of less than 10 mm. could only be obtained in one case out of five. Our readings were made under conditions far from ideal. The patients were nearly all exposed to the noise and bustle and changing temperature of an open ward. They were all sick, some of them desperately so, some of them had painful diseases, others were receiving subcutaneous medication every hour. It is not necessary to name over every external condition which might have had an influence on the pressure curve in these individuals. Under such conditions, variations of 10, 15 or even 20 mm. are to be expected as the result of unavoidable external stimuli, and unless very consistent, cannot be held up as evidence in favor of the view that the drug is increasing the activity of the vasomotor center, or that any other effect peculiar to the drug has been produced. The same reasoning applies to the rate of the heart-beat.

It is important to point out that the measurements we have made do not permit us to state directly whether the drugs examined increase the efficiency of the circulation. We are justified in doing nothing more than make cautious inferences about the matter from the data obtained. It is true that a very rapid pulse is an ominous sign in the acute infections and that an agent which can reduce the rate of the heart-beat under such conditions must be considered a valuable therapeutic possession. On the other hand, the fact that the pulse is not slowed by any given drug, does not necessarily mean that the drug may not be improving the circulation in other ways. It is equally true that rises of blood-pressure do not necessarily signify better circulation, and that an increased flow of blood may occur in the absence of any significant change in general blood-pressure.<sup>18</sup> It has been shown by Hooker<sup>19</sup> that increasing the pulse-pressure in the renal artery is followed by increased secretory activity on the part of the kidney, but it must be remembered that measuring the pulse-pressure in the brachial artery does not necessarily tell us anything about the pulse-pressure in the kidney or heart and that local changes in pulse-pressure are, in all likelihood, occurring in the organs according to the state of their activity.

With these limitations in mind, we present our data in Tables 1 and 2, and in the accompanying clinical histories and charts, and offer the following summary of the observations we have made.

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18. See for example, Price, F. E.: *Brit. Med. Jour.*, 1912, p. 689, and Sollmann and Pilcher, *loc. cit.*, Footnote 16.

19. Hooker, D. R.: *The Influence of Pulse-Pressure on Renal Function*, *Am. Jour. Physiol.*, 1910, xxviii, 24.

## SUMMARY

## STRYCHNIN

1. Eight times out of seventeen there was no change in systolic pressure. Once it fell 10 mm. for two hours. Nine times out of seventeen there was a rise in systolic pressure. This rise was small, usually brief, often of only a few minutes duration. It was inconstant, never to be relied on, often occurring after the first injection of a series, then falling to the original level in a short time and not recurring after subsequent injections. In no instance was the rise accompanied by improvement in the clinical condition. Only once was there a rise of more than 15 mm. In this single instance the pressure went up 26 mm. for a few minutes. In one patient the examination of the lungs caused a rise of from 20 to 30 mm. which lasted one hour; in another patient, subcutaneous injection of water caused a greater rise than  $\frac{1}{10}$  gr. strychnin.

2. Nine times out of thirteen there was no effect on the diastolic pressure. Once it fell 10 mm. for forty minutes. In another case 15 mm. for one and one-half hours. Once it rose 30 mm. for fifteen minutes.

3. Eleven times out of sixteen the pulse showed no change. In no case was there a slowing which could be honestly attributed to the drug.

## CAFFEIN

1. Eight out of nine times there was no effect on the systolic pressure. Once it fell 35 mm. during the period of treatment. There was not a single rise in systolic pressure as a result of administering caffein.

2. Five out of six times there was no effect on diastolic pressure. Once it fell 10 mm. during the period of treatment.

3. Nine out of ten times there was no effect on the rate of the pulse. Once it rose 10 beats per minute during the period of administration.

4. In no instance was there a measurable change in respiration.

A few cases deserve special comment. The failure of a large dose of strychnin, gr.  $\frac{1}{10}$ , to raise the pressure of a patient with tuberculous enteritis whose systolic pressure had been 80 to 95 mm. for several weeks, was considered highly significant.

A patient with delirium tremens, a frail, small woman, received  $\frac{1}{10}$  gr. of strychnin every hour for six hours, and after an interval of seven hours three more doses at the rate of  $\frac{1}{10}$  grain per hour, without showing either toxic symptoms or any blood-pressure change.

Case 23 is one of typical surgical shock induced by fracture of the skull. His initial systolic pressure, which was 55 to 65 mm., was unaffected by either  $\frac{1}{10}$  gr. strychnin or 5 gr. of caffein-sodio-salicylate. Nevertheless the failure of these drugs to show a pressor effect cannot be explained by assuming that the function of the vasomotor center was in abeyance, for stimulation of the peripheral nerves was followed by a prompt and lasting rise in the pressure of 30 mm. The stimulus consisted of scrubbing the wound with tincture of iodine. A similar condition was met in Case 12, in which two  $\frac{1}{10}$  gr. doses of strychnin, given within an hour, had no effect on the falling blood-pressure, but physical examination was followed by a rise of 40 mm.

### CONCLUSIONS

1. There is no evidence that the vasomotor apparatus is injured in the acute infectious diseases.
2. The evidence at hand does not permit us to say whether the functional activity of the myocardium is seriously impaired in the acute infectious diseases.
3. Strychnin sulphate, in medicinal doses, does not increase the output from the heart, slow the pulse or materially raise the blood-pressure. There is no logical basis for its use as a cardiovascular stimulant.
4. Caffein-sodio-salicylate, in the doses employed, does not raise the blood-pressure or slow the pulse. The method does not permit us to say whether caffein increased blood flow in the cases studied.

### CASE HISTORIES

CASE 9.—L. S., Pernicious anemia. Hgb. 30 per cent. Red cells 1,500,000. The patient complained chiefly of great weakness and anorexia. His temperature was slightly elevated and his pulse somewhat rapid. Examination of the heart showed the apex beat to be in the fifth space  $3\frac{1}{4}$  inches to the left of the midsternal line. The right border of dulness was  $1\frac{1}{4}$  inches to the right of the midsternal line in the fourth space. The upper border was at the third rib. The sounds were regular and of good quality. At the apex there was a short systolic and a faint diastolic murmur. At the base similar murmurs were heard. The pulmonic second sound equalled the aortic second sound in loudness and neither was accentuated. The patient was started on strychnin and in the course of four days received  $1\frac{4}{10}$  grains subcutaneously. There was no change in the cardiac or respiratory rate or in the blood-pressure. There was certainly no improvement in the subjective symptoms, and the patient lost 3 pounds during this period. The physical examination of the heart was as before the strychnin period.

CASE 10.—D. C., aged 23, typhoid fever. Moderately sick. Not in need of stimulation. Uneventful convalescence. On the third hospital day,  $\frac{1}{20}$  gr. of strychnin was followed by a rise in systolic pressure from 108 mm. to 118 mm. Two days later  $\frac{1}{10}$  gr. of strychnin was followed by a rise in pressure from 108 mm. to 115 mm.;  $\frac{1}{10}$  gr. of strychnin had no more effect than  $\frac{1}{20}$  gr. In both instances the systolic pressure was raised 10 mm. for less than one

hour. In the first instance the diastolic pressure did not change, consequently the pulse pressure was increased 10 mm. In the second instance the diastolic pressure fell 10 mm. with a resulting increase of 20 in the pulse-pressure. The rate of the pulse was not materially altered in either case. The strychnin caused no subjective sensations.

CASE 11 (Chart 1).—A. M. S., aged 16 years. Typhoid fever. Mild attack. Not in need of stimulation. The rise in both systolic and diastolic pressures following the strychnin is striking, but it will be noted that the systolic pressure remained 20 mm. higher throughout the day than it had been just before the strychnin, and that on the next day it was about 110, which was 10 mm. higher than the initial pressure. Such a prolonged effect could scarcely be attributed to the strychnin. On the second day after the strychnin, the early morning systolic pressure was again 100 mm. but rose during the day to 110 mm.; the next day the early morning pressure was 120 mm. In brief, the systolic

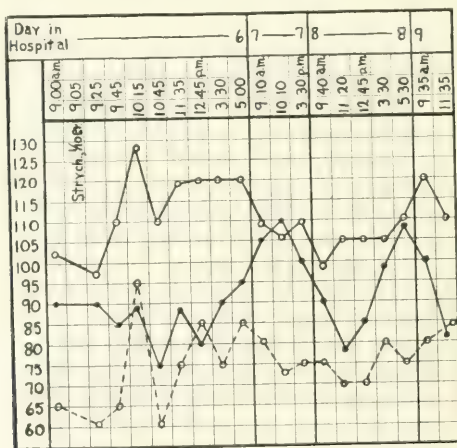


Chart 1 (Case 11).—In this and the following charts the temperature, pulse and respiration are represented in the usual way. The systolic blood-pressure is represented by circles connected by solid lines. The diastolic blood-pressure is represented by circles connected by broken lines. The dosage and the time of administration of the drug are printed on the chart (*Strych.* = strychnin sulphate).

blood-pressure of this boy, followed for three daws, showed a variation of twenty, due to influences of which we are ignorant. To attribute the rise of thirty on the first day entirely to the effect of strychnin would scarcely seem justified. It will also be noted that there was no increase in the pulse pressure following the giving of strychnin. The drug caused no subjective sensations.

CASE 12 (Chart 2).—A. J. G., aged 39. Lobar pneumonia. Not in need of stimulation. On the morning of the third hospital day he was given strychnin, gr. 2/10, subcutaneously. Up to this time the systolic pressure had been running between 135 and 145 mm. and the diastolic pressure about 100 mm. After

the dose of strychnin the systolic pressure fell to 122 and the diastolic to 90 mm. The next morning at 8 a. m. the systolic pressure was still 120, the diastolic 85 mm. At 8:30 a. m. the patient was examined, and at 9 a. m. the systolic pressure was 150 and the diastolic 110 mm. One hour later the systolic pressure was still 140 mm. It is evident that large doses of strychnin had no effect on a falling blood-pressure, and it is equally apparent that mild exertion did have a well marked pressor effect.

CASE 13.—P. T., aged 33. Lobar pneumonia. Not in need of stimulation. The systolic pressure had fallen progressively for the first three days in the

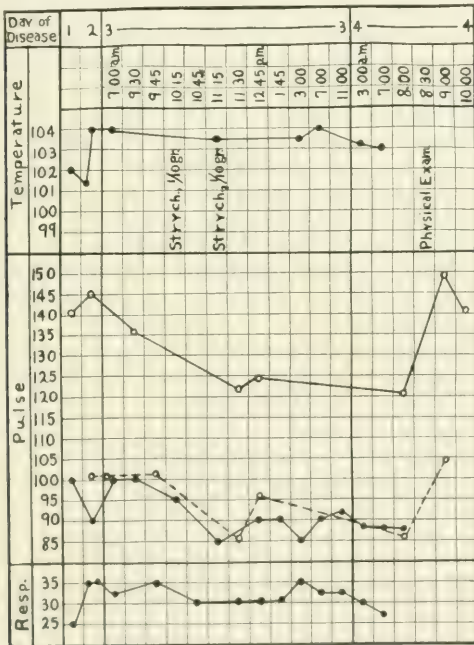


Chart 2 (Case 12).—Effect of strychnin sulphate (*Strych.*), as set forth in the case report.

hospital from 135 mm. to 120 mm. On the fourth day the patient was given strychnin sulphate, gr. 1/10, subcutaneously, at 12 noon and again at 1:30 p. m. No apparent change followed.

CASE 14.—F. MacD., aged 32, lobar pneumonia. At 4 p. m. and again at 5 p. m. on the fifth day of the disease, and the third in the hospital, the patient was given strychnin sulphate, gr. 1/10, subcutaneously. He was doing well at the time and not in need of stimulation. The systolic blood-pressure was, however, 105 mm., and so the attempt was made to raise it by means of large

doses of strychnin. The latter had no effect on either the systolic or the diastolic pressure, or on the rate or character of the pulse.

CASE 15 (Chart 3).—L. C., aged 56. Lobar pneumonia, fatal on the fourth day in the hospital. The patient was extremely sick at entrance and failed steadily in spite of various therapeutic efforts. On the first day she was started on digipuratum, gr.  $1\frac{1}{2}$ , three times a day, and camphor, gr. 3, subcutaneously,

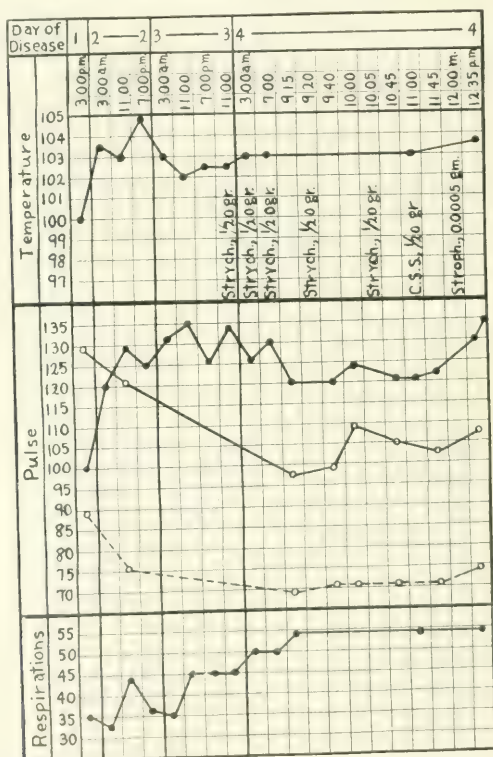


Chart 3 (Case 15).—Effect of digitalis, caffein-sodio-salicylate (C. S. S.) and strychnin sulphate (Strychn.) in a case of pneumonia.

each two hours, both of which were continued to the end. On the second day caffein, gr.  $1\frac{1}{2}$  each two hours was added. During the last twenty-four hours strychnin was given as shown on the chart. It will be seen that neither it, nor the camphor or caffein had any effect on the course of the disease.

CASE 16.—G. C. MacD., aged 25. Lobar pneumonia. Moderately sick. Not in need of stimulation. Systolic blood-pressure 110 mm., diastolic pressure



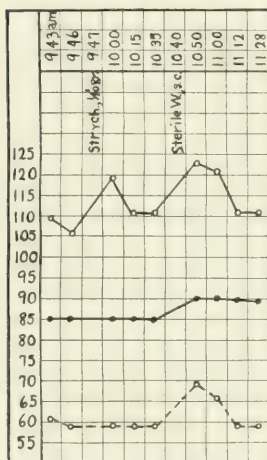


Chart 4 (Case 18).—Effect of strychnin sulphate (*Strych.*) in a case of chronic infectious colitis. *Sterile W. s. c.* = sterile water s. c.

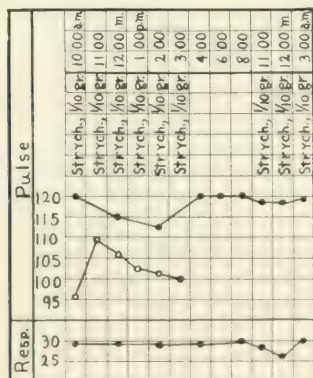


Chart 5 (Case 19).—Effect of strychnin sulphate (*Strych.*) in a case of fracture in an alcoholic.

80 mm. Strychnin sulphate gr. 1/20, subcutaneously, during the febrile period was followed by practically no change in the blood-pressure, but a slowing of the pulse, of twelve beats per minute. Strychnin sulphate, gr. 1/10, subcutaneously after the crisis, but while the pressure was still subnormal had practically no effect on the pressure or on the rate of the pulse. The strychnin caused no subjective symptoms.

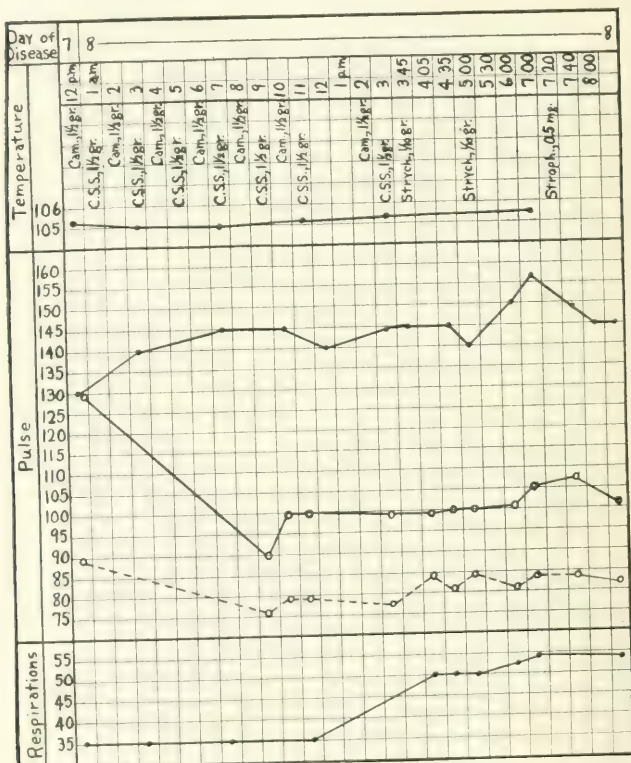


Chart 6 (Case 20).—Effect of camphor (*Cam.*) caffeine-sodio-salicylate (*C. S. S.*) and strychnin sulphate (*Strych.*) in a case of lobar pneumonia. *Stroph.* = strophanthin.

CASE 17.—J. B., aged 47, lobar pneumonia. The patient died on the third day in the hospital. Tincture of digitalis, minims 15, three times a day; camphor, gr. 1½ each two hours; caffeine-sodio-salicylate, gr. 1½ each two hours, alternating with the camphor, were given throughout the illness. On the third

day in the hospital when the systolic pressure was 110 mm. and the diastolic 75 mm. he was given 1/5 gr. of strychnin. No perceptible results followed.

CASE 18 (Chart 4).—C. A., aged about 25. Chronic infectious colitis. Marked loss of weight. Marked weakness. Not in need of stimulation. Following 1/10 gr. of strychnin the systolic pressure rose 12 mm. for fifteen minutes. The diastolic pressure did not change. A hypodermic injection of water was followed by a greater and somewhat more prolonged rise in systolic pressure, and a rise of 10 mm. in diastolic pressure.

CASE 19 (Chart 5).—N. R. A., aged 51. Fracture of the femur. Alcoholic history. Active delirium tremens. The chart shows what large amounts of strychnin may be given without producing any material or lasting change on systolic blood-pressure, pulse-rate, or respiratory-rate. The patient had 6/10 gr. of strychnin in six hours and a total of 9/10 gr. in seventeen hours without showing any toxic symptoms or even a slowing of the pulse.

CASE 20 (Chart 6).—F. O., aged 41. Fatal lobar pneumonia. Several hours after entrance to the ward the systolic pressure was 130, the diastolic pressure 90 mm., and the pulse-pressure 40. The next morning the systolic pressure had

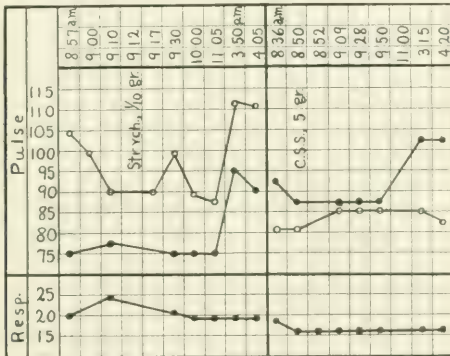


Chart 7 (Case 21).—Effect of strychnin sulphate (*Strych.*) and caffein-sodio-salicylate (*C. S. S.*) in a case of tuberculous enteritis and peritonitis.

fallen to 90-100, the diastolic to 75-80, and the pulse-pressure to 15-20 mm. Hg. During the night she had received camphor, gr. 1½ subcutaneously each two hours for five doses, and caffein, gr. 1½ each two hours for five doses. Between 10 a. m. and 2 p. m., and again between 2 p. m. and 6 p. m. she had had no camphor. There was, however, no fall in blood-pressure or rise in pulse. Between 11 a. m. and 5 p. m. she had had but one dose of caffein. There was, however, no fall in blood-pressure or rise in pulse. This would seem to indicate that neither the blood-pressure nor the pulse had maintained the level recorded earlier in the day because of the administration of the drugs. At 3:45 p. m. she was given strychnin, gr. 1/10 subcutaneously without effect on the pulse or the blood-pressure. Following strophanthin at 7:20 p. m. there was a slight slowing of the pulse and a slight rise in blood-pressure. The patient died at 3:30 the next morning.

CASE 21 (Chart 7).—A. X., aged about 32. Tuberculous enteritis and peritonitis. Diarrhea of four months' duration. Great loss of weight. Marked weakness and emaciation. Irregular afternoon rises of temperature. The sys-



dent had resulted in a fracture of the skull in the left frontal area. The patient was conscious but lethargic and in no pain. He was able to give his name. His skin was cold and colorless and his lips were blue. The systolic blood-pressure was 55-65 mm. Pulse was small but regular and slow. His heart sounds were not remarkable. His pupillary reflexes and knee-jerks were present. Neither strychnin sulphate, gr. 1/10 subcutaneously, nor caffein-sodio-salicylate, gr. 5 subcutaneously, had any effect on the blood-pressure, pulse or general condition. At 9:45 p. m., about two and one-half hours after being in the hospital, a piece of ice was placed on his abdomen for thirty seconds to see whether marked external stimuli (cold) would have any effect on the systolic pressure. None was observed. At 10 p. m. his wound was scrubbed with tincture of iodine.

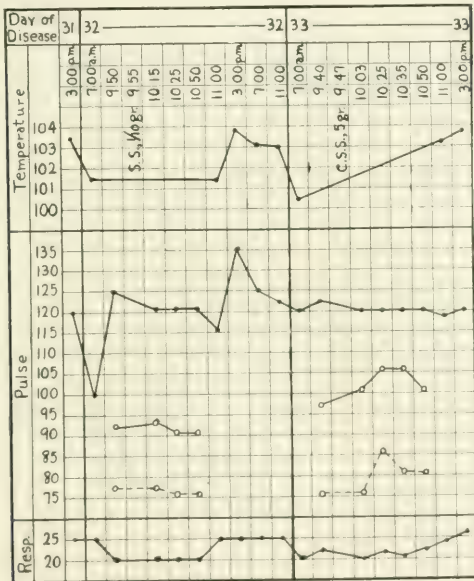


Chart 9 (Case 24).—Effect of strychnin sulphate (S. S.) and caffein-sodio-salicylate (C. S. S.) in a toxic case.

This caused a great deal of pain and resulted in an elevation of the systolic pressure, at first to 85 and then to 95 mm. This rise in pressure was taken to mean that the vasomotor center was not paralyzed, but was still capable of responding to stimuli, if sufficiently great, and that consequently the failure of the drug to cause a response could not be explained by the assumption that the center was paralyzed. The next morning the patient had entirely recovered from the shock. He was rational and alert and expressed a great desire for food. His systolic pressure was 95 and his diastolic 65 mm.

CASE 24 (Chart 9).—P. M., aged 49. September 15, entered the hospital after one week's illness. September 27, very toxic. September 30, still more

toxic; low muttering delirium. October 5, the pulse was recorded at 170 for several hours. No hemorrhage at any time. October 16 and 17, strychnin and caffein were given. The strychnin was followed by practically no change in the cardiac or respiratory rates or in the blood-pressures. Caffein was without effect on the cardiac or respiratory rates and the very moderate changes in the systolic and diastolic pressures resulted in a lessening of pulse-pressure. The pulse showed a well marked respiratory rhythm and a slight irregularity in volume. Neither of these qualities was affected by the drugs. The patient had been very sick for some days preceding October 16, but was not losing ground and was not in direct need of stimulation when the above mentioned drugs were administered.

CASE 25.—J. G., aged 24. August 20, fever, rapid pulse, leukocytosis, multiple pyemic abscesses. Operation. Did not pick up following operation. September 6, right shoulder joint incised. September 10, growing worse. No hope for recovery. From September 5 to 8, caffein-sodio-salicylate, gr. 2, each two hours subcutaneously, and camphor, gr. 3, each two hours subcutaneously, had been given. September 8 the camphor was omitted, because it was thought that it was doing no good, and the caffein was reduced to gr. 1. September 11, blood-pressure readings were started. September 12, administration of 5 grains of caffein was without effect on the blood-pressure, the rate of pulse, or the rate of the respiration.

September 21. Since the last note the patient has been failing steadily. He looks as if he were about to die. Caffein, gr. 5, followed by gr. 3, was without effect on the blood-pressure. The pulse, however, fell 25 beats. This fall can scarcely be attributed to the drug, because the pulse had been at the lower level earlier in the morning. Shortly before the 10:45 a. m. reading, a painful dressing had been done. The pulse-rate increased in response to this and in the natural course of events it fell again to its previous level. Caffein was purposely given at this time to emphasize the care that must be exercised when judging of the effect of a drug under these complex conditions. The respiration became distinctly slower, following the administration of the drug, and there is no evidence to show that this was not a caffein effect. September 22, the patient received 17 grains of caffein in eight hours. It was without apparent effect on the respiratory or cardiac rates. September 23, died.

CASE 26.—A. P., aged 40. Traumatic compound fracture of right tibia and fibula. Fracture of right femur. He was brought to the hospital at 9:45 a. m., two hours after the accident, in surgical shock. He was given morphin sulphate, gr.  $\frac{1}{4}$  subcutaneously, on entrance. The systolic blood-pressure was 85 mm., diastolic 50 mm., pulse 62, and the respiration 18. At 10:35 a. m., 5 gr. of caffein were injected. No measureable effect followed.



## IMMUNITY TESTS IN COCCIDIOIDAL GRANULOMA\*

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SAN FRANCISCO

Human infection by the organism now known as *Coccidioides immitis* was first reported in 1892 by Posadas and Wernicke in Buenos Aires. These observers regarded the parasites as protozoa, but later (1896) Rixford and Gilchrist gave the organism the binominal designation of *Coccidioides immitis*, and Ophüls succeeded in obtaining pure cultures in 1900. Other cases have been recognized from time to time, and recently MacNeal and Taylor<sup>1</sup> have collected twenty-four cases from the literature. In one of these reported by Brown, however (Case 18), the diagnosis was not confirmed culturally or by microscopic examination. All the reported cases except the first have occurred in the United States, and in a large proportion of them the infection can be traced to the San Joaquin Valley in California. The disease affects chiefly adult males, only one woman and one child being included in the cases observed. Only two patients are known to have recovered.

The infection is characterized by the formation of successive nodular or suppurative foci which may affect any part of the body, but more often are localized in the bones and joints, lymph-nodes, lungs and skin. The clinical symptoms depend on the anatomical distribution of the lesions. Histologically, the process resembles tuberculosis and belongs to the group of the infectious granulomata, the disease usually being termed, therefore, coccidioidal granuloma. In sections and in pus from the lesions the organism occurs as refractile, doubly-contoured, spherical bodies varying from 3 to 50 microns in diameter. These differ from the parasites found in blastomycosis in that budding forms are never seen in the animal body. In the tissues *Coccidioides immitis* multiplies by endosporulation and mycelium is never found, but when transplanted on artificial culture mediums the spherical bodies form mycelium almost immediately. Growth appears usually in less than a week and is more rapid at incubator temperature. Preparations from cultures show septate branching hyphae on which after a period of time chlamydospores develop. Dogs, rabbits and guinea-pigs can easily be infected with pus from one of the lesions or with emulsions from cultures. For more details concerning the clinical, pathological

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\* Submitted for publication Sept. 29, 1914.

<sup>1</sup> From the Pathological Laboratory of the University of California Hospital.

1. MacNeal and Taylor: Jour. Med. Research, 1914, xxx, 261.

and microbiological features of the infection reference may be made to the papers of Ophüls,<sup>2</sup> Wolbach,<sup>3</sup> Hektoen,<sup>4</sup> Brown<sup>5</sup> and MacNeal and Taylor.<sup>1</sup>

The purpose of this paper is to add two other cases to the list of those already observed, and to report the results of a series of experiments designed to demonstrate specific immune substances in the blood of one of these patients.

#### CASE REPORT

*History.*—A Portuguese man (M. M.), aged 25, was admitted to the surgical wards of the University of California Hospital, Dec. 1, 1913, with multiple abscesses. He was born in the Azores Islands, but had been in this country for many years. During the three months preceding his present illness he had been employed as a milker on a ranch near Newman, Cal. (San Joaquin Valley). His family history and past history were both negative. He remembered no previous illnesses and had not been associated, so far as he knew, with anyone affected with ulcerations on the skin or with abscesses.

The history of his illness follows: About nine months previous to admission he noticed a painful lump on his right wrist. This was opened by a physician and exuded pus for a considerable length of time. Later his right knee began to swell and after three months suppurated. It was aspirated by another physician and placed in a plaster cast, but as the rapid suppuration continued he was removed to a hospital and the joint was resected. The wound did not heal after this operation but continued to discharge pus. During this time other suppurative foci appeared over the right shoulder, left arm, left ankle below the external malleolus, and two foci beneath the scalp.

*Physical Examination.*—On admission (Dec. 1, 1913) the right knee showed numerous sinuses and the resected joint was mobile and painful; the right foot showed a sinus at the first distal metatarsal joint, running up the inner side of the foot to an ulcer over the Achilles tendon; the right wrist was riddled with sinuses discharging pus, the carpus seemed disintegrated and the lower end of the radius was swollen; left foot showed a discharging sinus below the outer malleolus, the left ulna was thickened and just below its middle showed a painful soft fluctuating mass about 6 cm. in diameter; two sinuses in the scalp ran down to the skull, one over the frontal bone just to the right of the median line and the other about 7 cm. posterior to the first; the left knee joint was distended and painful. The ulcerated areas at the sinus openings showed flat irregular granulations at the edges and were bathed in a purulent secretion.

The patient appeared considerably emaciated and was quite weak. Physical examination was otherwise negative except for a moderate enlargement of the cervical, axillary and inguinal lymph-nodes and a slightly impaired resonance at the left pulmonary apex.

*Course.*—The left knee gradually became more swollen and was aspirated several times. December 24 it was opened and 1,000 c.c. of pus removed. During the next two months the patient became weaker and more emaciated, all the lesions continued to discharge abundant purulent material, and new suppurative foci appeared on the left hip, right axilla and left shoulder.

March 8 the patient left the hospital against advice. He died a few days later and no necropsy was permitted.

2. Ophüls: Jour. Am. Med. Assn., 1905, xlv, 1291.

3. Wolbach: Jour. Med. Research, 1904, xiii, 53.

4. Hektoen: Jour. Am. Med. Assn., 1907, xlix, 1071.

5. Brown: Jour. Am. Med. Assn., 1907, xlviii, 743.

During his stay in the hospital his temperature ranged between 37 and 38 C., and the leukocytes varied from 12,000 to 20,000; hemoglobin was 46 to 60 per cent. (Dare); urine was negative for sugar and albumin. Blood-cultures taken on three occasions were negative. Wassermann was negative. The spherical doubly-contoured organisms were demonstrable in fair numbers in every specimen of pus examined. One specimen of sputum was reported to contain coccidioides, but this could not be verified as no more sputum could be obtained.

*Medication.*—Two doses of neosalvarsan, 0.6 gm., were given intravenously and also large doses of potassium iodid, without any apparent effect.

*The Parasite.*—Numerous examinations of pus from the various lesions showed pus cells and rather numerous refractile doubly-contoured spheres which varied considerably in size; some were no larger than a red blood corpuscle, while the largest one measured was 40 microns in diameter. All gradations between these sizes were seen. The spheres were for the most part composed of a coarsely granular protoplasm in which little structure could be distinguished. Some cells, however, appeared filled with small spheres each of which had a sharply defined individual capsule, and occasionally the smaller bodies could be seen escaping from one of these sporangium-like forms. No budding forms were ever observed.

Cultures at incubator temperature showed a definite tenacious growth at the end of twenty-four hours, which after a few days spread over the whole surface. Old cultures, especially those kept at room temperature, developed abundant aerial hyphae and appeared fluffy. In block preparations on glucose agar, the spore-like bodies from the pus at the end of twenty-four hours showed thread-like outgrowths of mycelium which later became branched and segmented. In older cultures the extremities of the segments became bulbous or clubbed and chlamydo-spores developed on some of the hyphae.

Male guinea-pigs were inoculated both with a few drops of pus from one of the lesions and with a small amount of an emulsion of a two-months-old agar culture. After a few weeks there occurred in both cases the typical marked enlargement of the testes and the animals were killed. At autopsy suppurative foci were found in the testes, lungs and liver, from which the spherical doubly-contoured bodies were readily demonstrable and pure cultures were recovered.

The patient was an Italian man aged 29, and the history obtained was very meager. Nine months previous to his admission, while at Bakersfield (San Joaquin Valley), he noticed a swelling of the cervical glands. He had been treated for some time in a tuberculosis sanatorium.

Physical examination showed an emaciated man who breathed with difficulty on account of large nodular masses in the neck. On the forehead above the left eye was a large sinus about 4 cm. in depth from which thick yellowish pus was discharging.

At the base of this sinus was necrotic bone. On the left shoulder were two discharging sinuses which extended beneath the clavicle and a similar open sinus was present in each supraclavicular fossa. In the neck extending downward from the angles of the jaw and in the posterior cervical triangles could be felt large, somewhat softened nodular masses. Both lips showed several healed scars. Aside from the special lesions noted, physical examination was negative. On the fourth day after admission the patient died from asphyxiation. Examination of pus from the discharging lesions showed numerous refractile spherical, doubly-contoured bodies, varying somewhat in size, but as a rule about three times as large as a pus cell. Many of these spheres were apparently filled with numerous small spore-like bodies. No budding forms could be found. Cultures gave a mold-like growth.

An additional case of coccidioidal granuloma was observed in July, 1914, at the Santa Clara County Hospital, San Jose, Cal., by Dr. Elizabeth G. Lewis, to whom I am indebted for the following clinical and post mortem notes:

At necropsy the numerous walnut-sized masses in the neck noted in the clinical examination were abscesses filled with yellowish pus, and there was also a large postpharyngeal abscess containing similar material. The apex of each lung was firmly bound by adhesions and formed part of the wall of an abscess which was discharging through a sinus above the clavicle. Section of the lung itself, however, showed no gross lesion and nothing noteworthy was noted in the examination of the rest of the viscera.

Tissue saved for microscopic study was unfortunately thrown away by mistake. The only material available for examination was an agar culture from the pus. This corresponded in all respects to the cultures of *Coccidioides immitis* from the case above described.

#### ANTIBODIES

This patient was under observation for some time and attempts were made to ascertain what demonstrable antibodies were formed in response to the infection. The antigens used for this purpose were made from the strain of *Coccidioides immitis* obtained from the patient and consisted of the two forms of the organism—(1) the mycelial growth from artificial culture mediums, and (2) the spore-like bodies from one of the purulent lesions. The mode of preparation of these antigens was as follows:

1. *Antigen from mycelial growth.*—A considerable number of agar cultures of *Coccidioides immitis* about four weeks old were used. The cotton plugs were treated with a few drops of formaldehyd solution and sealed. After twenty-four hours the tenacious growth was removed with a platinum spatula and dried over sulphuric acid. It was then powdered by grinding for several hours in an agate mortar.

2. *Antigen from the organism in the body.*—One thousand cubic centimeters of rather thick pus from an abscess (knee) was treated with 162 c.c. of anti-formin and allowed to stand with occasional shaking for five hours. It was then centrifuged and the sediment washed five times with 0.85 per cent. NaCl solution, after which the reaction was neutral to litmus. Microscopic examination showed that the sediment was composed almost entirely of the spherical doubly-contoured bodies. Cultures remained sterile. This sediment was dried over sulphuric acid and the residue ground for several hours in an agate mortar. A second specimen of 500 c.c. of pus was similarly treated with anti-formin, centrifuged and washed. A rather thick emulsion of the spherical bodies was made in 0.85 per cent. NaCl solution. This latter was used in the agglutination tests and was also used as antigen in some of the complement fixation tests.

*Controls.*—A similar powder was made in exactly the same manner from cultures of a strain of blastomyces from one of the Chicago cases. This organism showed many budding forms in culture in addition to mycelial growth.

Normal serums used in all the controls were from ambulatory patients not suffering from any infectious disease.

#### COMPLEMENT FIXATION TESTS

The antigens used for these tests consisted of 0.5 per cent. emulsions of the powdered growth of coccidioides and blastomyces in 0.85 per cent. NaCl solution and in addition an emulsion of the spore-like forms of coccidioides obtained from the pus. A rabbit-antisheep

hemolytic system was used in all tests and the complement and hemolysin were always titrated before use. In the tests the inactivated patient's serum with antigen and  $1\frac{1}{2}$  units of complement were incubated for one hour and then two units of hemolysin (1:2,000) and 1 c.c. of a 5 per cent. suspension of sheep corpuscles added. The tubes were reincubated for two hours and placed in the icebox. The final readings were made the following day. Two normal serums were used as controls. On titration it was found that the emulsions of the dried mycelium of *coccidioides* inhibited hemolysis in amounts larger than 0.07 c.c., and that of *blastomyces* in amounts larger than 0.05 c.c., while the *coccidioides* "spores" did not inhibit in dilutions of 0.3 c.c. Varying amounts of serum up to 0.5 c.c. were tested and the results were entirely negative. Another similar series was carried out, using inactivated serum collected the same day the tests were done. This also gave negative results.

#### CUTANEOUS REACTIONS

Since certain antigens like tuberculin, typhoidin and others cause a specific skin reaction, it was thought of interest to try similar reactions with *coccidioides* in the present case. Boughton and Stober<sup>7</sup> have reported an apparently specific skin test in a case of blastomycosis, although it is stated that the patient was recovering from the infection at the time the test was done. Davis,<sup>8</sup> however, was unable to obtain a positive skin reaction in guinea-pigs experimentally infected with a similar organism. In applying the tests both the intradermal method and scarification with a von Pirquet chisel were used. The following antigens were employed in each test: (1) A rather thick suspension of the powdered mycelial growth of *coccidioides* suspended in 0.85 per cent. NaCl solution; (2) a 5 per cent. glycerin emulsion of the same dried powder concentrated to one-tenth its original volume; (3) a concentrated glycerin bouillon filtrate from a four-weeks-old *coccidioides* culture prepared in a manner analagous to that used for making "old tuberculin"; (4) a rather thick suspension in 0.85 per cent. NaCl solution of the powdered spherical bodies from the pus; (5) and (6) suspensions of dried *blastomyces* growth prepared in a similar manner to (1) and (2). Controls of 0.85 per cent. NaCl solution and 50 per cent. glycerin were also used. A small drop of each of these was placed on a small area of scarification on the skin of the arm made with a von Pirquet chisel and allowed to dry. If the material had not dried at the end of five minutes, the excess was gently removed with absorbent cotton. No indication of any reaction appeared around any of

7. Boughton and Stober: THE ARCHIVES INT. MED., 1914, xiii, 599.

8. Davis: Jour. Infect. Dis., 1911, viii, 190.



the areas in the five succeeding days. The tests were repeated one month later and on two control cases with the same result.

In the intradermal tests, a very small amount of each of the antigens was injected in the superficial layers of the skin of the arm. In all except the controls and (3) the concentrated broth filtrate, there was formed an indurated red area of reaction from 5 to 10 mm. in diameter which at the end of forty-eight hours became pustular. The pus was sterile and the lesions had practically disappeared at the end of a week. This same reaction occurred in six control patients on whom the same tests were done and undoubtedly resulted from irritant substances present in the organisms themselves. The same tests were repeated after the various antigens had been diluted until no reaction was caused in control patients and the diluted antigens caused no reaction in the case of coccidioid granuloma.

#### AGGLUTINATION TESTS

The suspensions of coccidioides used in these tests were obtained as above described by treating a specimen of pus with antiformin, and consisted of a considerable number of the spherical doubly-contoured bodies in salt solution. The hanging drop method was used and two series of preparations made; one was incubated at 37 C. and the other left at room temperature. The dilutions made of the serum were 1:5, 1:10, 1:20, 1:40 and 1:80, and in each experiment the mixtures were made of (1) immune serum plus suspension, (2) normal serum plus suspension, and (3) salt solution plus suspension. Both the incubated series and that left at room temperature were examined at intervals of one hour for the first six hours, and again at the end of twenty-four hours. The results were entirely negative.

#### PRECIPITIN TESTS

For these tests 0.3 gm. of the powdered mycelial growth of coccidioides was thoroughly ground with 30 c.c. of 0.85 per cent. NaCl solution to which 0.5 per cent. phenol had been added. This suspension was allowed to stand for several days, being shaken at intervals, and then centrifuged. The faintly opalescent supernatant fluid was employed in the tests. Similar extracts were made from the powdered coccidioides "spores" and from dried blastomyces cultures.

The first series of tests was carried out by stratifying the antigen above the serum in such a manner as to give a sharp line of contact. The tubes were incubated and readings made at the end of one hour and two hours. The various antigens were used in their full strength and also diluted 1:2, 1:5, 1:10 and 1:20, with 0.85 per cent. NaCl solution. As controls a solution of 0.85 per cent. NaCl solution with



0.5 per cent. phenol and normal serums were used. In all, serums from twelve control patients were tested. Table 1 gives the results of these experiments.

Another series of precipitin tests was carried out in the usual way by mixing various amounts of serum with the same antigens used in the previous experiment. The technic used was as follows: Varying amounts of clear serum from the patient with coccidioidal granuloma were added to a constant amount of the antigen extracts in small test-tubes and the mixture diluted to a uniform volume by the addition of 0.85 per cent. NaCl solution. The tubes were then incubated for two

TABLE 1.—RESULTS OF PRECIPITIN TESTS

Extract, 0.5 c.c.	Serum from Case of Coccidioides, 0.5 c.c.	Normal Serum * 0.5 c.c.
Coccidioides culture .....	Heavy ring	No precipitate
Coccidioides 1:2½ .....	Distinct ring	No precipitate
Coccidioides 1:5 .....	Faint ring	No precipitate
Coccidioides 1:10 .....	No precipitate	No precipitate
Coccidioides 1:20 .....	No precipitate	No precipitate
Coccidioides "spores" .....	Distinct ring	No precipitate
Coccidioides "spores" 1: 2½ ..	Faint ring	No precipitate
Coccidioides "spores" 1: 5 .....	No precipitate	No precipitate
Coccidioides "spores" 1:10 ....	No precipitate	No precipitate
Coccidioides "spores" 1:20 ....	No precipitate	No precipitate
Blastomyces .....	No precipitate	No precipitate
Blastomyces 1: 2½ .....	No precipitate	No precipitate
Blastomyces 1: 5 .....	No precipitate	No precipitate
Blastomyces 1:10 .....	No precipitate	No precipitate
Blastomyces 1:20 .....	No precipitate	No precipitate
NaCl solution 0.85 per cent. + phenol 0.5 per cent. ....	No precipitate	No precipitate

\* Eleven other normal serums were tested with the same result.

hours at 37 C. and placed in the ice-chest. The readings were made at the end of twenty-four hours. The usual controls were introduced as may be noted from Table 2.

#### SUMMARY

In a case of coccidioidal granuloma studied no specific complement-fixing bodies or agglutinins could be found in the blood-serum using cultures of *Coccidioides immitis* and emulsions of the same organism from human lesions as antigens. No specific skin reaction could be demonstrated. Precipitins, however, could be demonstrated in the serum even when diluted 1:160, when an extract of dried cultures of the organism was used as precipitinogen. These precipitins were apparently specific, since they could not be demonstrated when normal

serum was tested with the same antigen or when the specific immune serum was tested with an antigen similarly prepared from the closely related organism, blastomyces.

The presence of specific precipitins in this infection must be verified by the examination of other cases. It is suggested that this reaction might be applied as a means of diagnosis in cases of deep-seated infec-

TABLE 2.—ADDITIONAL PRECIPITIN TESTS

	Extract Coccidioides Culture	Extract Coccidioides "Spores"	Extract Blastomyces Culture	NaCl Solution 0.85 Pct.
Immune serum 1: 10 .....	+	+	0	0
Immune serum 1: 20 .....	+	+	0	0
Immune serum 1: 40 .....	+	+	0	0
Immune serum 1: 80 .....	+	0	0	0
Immune serum 1: 160 .....	+	0	0	0
Immune serum 1: 320 .....	0	0	0	0
Normal serum 1: 10* .....	0	0	0	0
Normal serum 1: 20 .....	0	0	0	0
Normal serum 1: 40 .....	0	0	0	0
Normal serum 1: 80 .....	0	0	0	0
Normal serum 1: 160 .....	0	0	0	0
Normal serum 1: 320 .....	0	0	0	0
NaCl solution 0.85 per cent. and phenol 0.5 per cent. ....	0	0	0	0

+ = precipitate; 0 = no precipitate.

\* A series of nine other normal serums was tested with negative results.

tion where there are no discharging lesions from which the spherical doubly-contoured bodies can be demonstrated. It might also serve as a means of differentiating coccidioidal granuloma from blastomycosis in obscure cases.

Experiments are now being carried out to determine whether specific immune substances are formed in infected animals.

36 Farnsworth Lane.

## THE VALUE OF THE ELECTROCARDIOGRAM IN THE DIAGNOSIS OF CARDIAC HYPERTROPHY \*

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The steady increase in the number of electrocardiographs, their constant clinical and experimental application, together with the resulting advance in the knowledge of cardiac activity, all go to show the need and importance of this method of investigation. The exactness of the instrument in the diagnosis of any of the arrhythmias, and the simplicity of technic make it indispensable in any large clinic, where it tends to supplant the polygraph. When any new technical method is devised, be it in bacteriology, physics or diagnosis, it is at once applied to different problems in the constant effort towards the establishing of new truths. In such a way the electrocardiogram has come to be applied in an ever-widening field of cardiac investigation; and, among other uses, it has come to be a method for the determination of hypertrophy of the right and left sides of the heart. There must, of necessity, be a constant balancing of methods and results in order that the usefulness of a method be ascertained and that further progress be securely established.

To this end it was thought worth while to review the electrocardiograms obtained in the past few years at the Johns Hopkins Hospital, in an effort to compare the clinical findings, supplemented as they are by radiographic, fluoroscopic, and post-mortem knowledge, with the information obtained from the electrocardiogram. For this purpose some two hundred cases were taken, and their discussion will be the purpose of this paper. They include cases of clinical right- or left-sided hypertrophy with normal electrocardiograms, cases with apparently normal hearts with electrocardiographic findings of hypertrophy, and cases of apparently normal hearts from both the clinical and laboratory points of view.

At this point it would seem *apropos* to say just a word as to the physiological significance of the electrocardiogram. The different views, now current, only confirm the conception that the interpretation of the various peaks is by no means definite. Thus, is the "R" wave of papillary origin? Does the "T" wave result from contraction of a ring of muscle at the root of the aorta? Or, indeed, following Eyster's lead, does the "R" wave represent excitation and the "T" wave signify

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\* Submitted for publication Oct. 28, 1914.

contraction? To avoid a technical paper and to limit it to the clinical point of view, such conceptions will not be discussed. It will suffice to sum up the general opinion—to regard the "P" as of auricular origin and the "QRST" complex representative of ventricular activity, where any one point on the curve represents the algebraic sum for the particular derivation of the electrical potentials throughout the heart at that instant of time. The relative potential of the different sides of the heart change with the lead employed, so that the type of curve obtained in the left-arm and left-leg derivation is quite different from that obtained from the left-leg and right-arm. Furthermore, it would seem possible that different cardiac conditions—as relative hypertrophy of one side, change of the position of the heart—would be reason for changes in the ratio of the electrical potentials expressed by the electrocardiogram. Again, a thousand and one extra-cardiac conditions must be considered—the electrical conductivity of different tissues, the character of the retromanubrial tissue, the position of the body, the condition of the surrounding organs which might dislocate the heart. The age of the patient must be remembered, as the heart of a child is relatively larger than that of an adult, and then, with advancing age, varying degrees of sclerosis with varying cardiac responses develop.

Following hypertrophy of the left side of the heart, it is only too evident that a relative right-sided hypertrophy will result of an amount determined by the extent and duration of the original lesion and the reserve force on the right side. It would seem, then, that not only is the diagnosis of a pure left- or right-sided hypertrophy very difficult, but, a point much more fundamental, it is well nigh impossible to set up a physiological standard, and the term "normal" as applied to the cardiovascular system is very indefinite and, at best, is relative and varies with the individual. The standardization of the electrocardiogram based on such variability is difficult, and its diagnostic value decreases proportionately.

For the purpose of study, however, let us assume the general opinion that the normal electrocardiogram is one with no progressive increase or decrease in the size of the "R" wave in the three derivations—that left ventricular hypertrophy would give an "R" wave which would be shorter in "D<sub>2</sub>" than in "D<sub>1</sub>," and still shorter or inverted in "D<sub>3</sub>." While the reverse—a progressive increase in the height of the "R" wave from "D<sub>1</sub>" through "D<sub>2</sub>" to "D<sub>3</sub>"—is that associated with right ventricular hypertrophy. The absolute ignorance of the significance of the "Q" and "S" waves precludes their discussion.

At first in collecting normal cases, individuals of different ages were taken. They were non-patients and were presumably normal. But among these were found left- and right-sided hypertrophy, as well

as normal appearing electrocardiograms. This at once necessitated careful physical examination and a knowledge of their cardiac history; did they have athletic hearts, was there arteriosclerosis, or beginning chronic nephritis? To obtain a thorough physical examination and to avoid the personal element, it was thought fairer to cull from the hospital records non-cardiac cases that had electrocardiograms, and whose physical examination, made by different investigators, and often confirmed by roentgenography, or occasionally by post mortem, had disclosed normal sized hearts. Thus, fifty cases were obtained of clinically normal hearts, in which there was no apparent lesion of the cardiovascular system, and in which there was no demonstrable etiological factor which might lead to cardiac enlargement. These cases were diagnosed as neurasthenia, chronic appendicitis, gastric anacidity, and the like, and, in all of them, careful examination showed no cardiac abnormalities. Needless to say, that routine examinations by several men are more trustworthy than that made by one, and it would seem that such cases would be much more adaptable for the establishing of a norm than fifty persons taken off the street, so to speak, in whom the history and routine study would be much less complete.

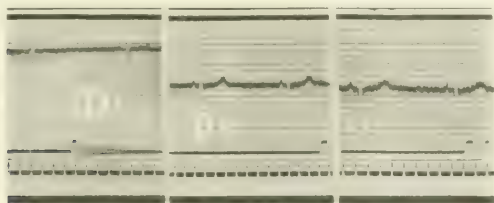


Fig. 1.—Right ventricular hypertrophy from the electrocardiogram with a clinically normal heart. Patient aged 15.

There were ten patients of ages varying from 10 to 20, who, as far as could be ascertained, were normal. Seven of these were boys from private schools who were taken in connection with heart-sound work, and whose physical examinations, checked by Dr. Thayer and Dr. Bond, were in no way remarkable. The other three patients of this age were hospital cases—*dementia praecox* and *neurasthenia*. Eight of these ten showed electrocardiographic findings of right ventricular hypertrophy. The others gave the normal sequence of derivations.

M. F., aged 15, diagnosed as having *psychoneurosis*, *anorexia nervosa*, *dementia praecox*, was a tall, thin girl weighing 55 pounds. She showed a normal venous-pulse. The apex was in the fourth interspace, 6 cm. from median sternal line, and the cardiac dulness extended 8.5 cm. to the left and not to the right of the median sternal line. The rest of the physical examination was

not remarkable, blood-pressure being 90, and the urinary findings normal. The Roentgen ray disclosed a heart in normal position and of normal size, which by actual measurement, corresponded closely to the clinical dimensions. The electrocardiogram as shown in Figure 1 is typically that of right ventricular hypertrophy.

Perhaps she did have a relative right ventricular hypertrophy, but it could hardly be regarded as pathological. That such a sequence of derivations is the normal at this age is also possible, but it is by no means constant, as two of the patients of this age did not show a progressive increase in the height of the "R" wave. The difficulty of

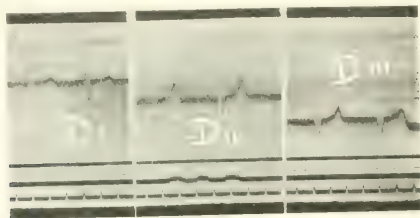


Fig. 2.—Right ventricular hypertrophy from the electrocardiogram with a clinically normal heart. Patient aged 14.

assuming a standard is at once evident, and without a standard the diagnosis of the pathological becomes, of necessity, indefinite. Six of the schoolboys showed the sequence of derivation associated with right ventricular hypertrophy, as seen in Figure 2, and one of the same age,

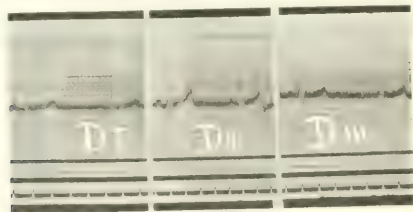


Fig. 3.—Normal sequence of derivation in a clinically normal heart. Patient aged 15.

again with normal cardiac findings, had, according to the electrocardiogram (Fig. 3) a normal relation of ventricular potentials in the three derivations.

In the same way there were fourteen whose ages varied from twenty to thirty—a group evidently useless in drawing statistical conclusions, but sufficient to show the lack of uniformity. Again the physical find-



ings were normal, and the diagnoses were psychoneurosis and neurasthenia. Eight showed normal electrocardiograms, three showed right-sided and three showed left-sided ventricular hypertrophy.

Mrs. L. H., aged 26, with a diagnosis of psychoneurosis, psychasthenia, and a questionable pulmonary tuberculosis, showed indefinite signs at the right base with a negative Calmette, and, according to Roentgen ray findings, some fibrosis of the lung. Her apex was in the fifth interspace, well within the midclavicular

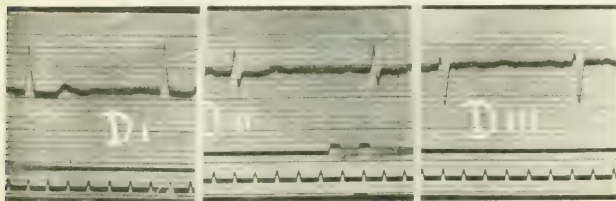


Fig. 4.—Electrocardiographic findings of left ventricular hypertrophy with a clinically normal heart. Patient aged 26.

line. Her cardiac dullness extended 3 cm. to the right and 9.5 cm. to the left of the median sternal line. Her blood-pressure was 125 and there were normal urinary findings. The Roentgen ray showed a normally placed heart of normal dimensions. The electrocardiogram of this patient (Fig. 4) showed marked left ventricular hypertrophy with "S" wave very marked in "D<sub>1</sub>" and the "R" inverted markedly in "D<sub>3</sub>." That is, a case of left ventricular hypertrophy according to the electrocardiogram, with, clinically, a normal heart.

It might be that this marked left ventricular hypertrophy is significant of early cardiac changes which would not be so prominent, as, with later developments, right ventricular changes appeared to cloak the present electrocardiographic signs. But, occurring as it does, with

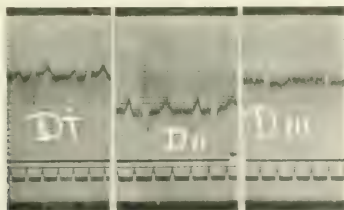


Fig. 5.—Electrocardiographic findings of right ventricular hypertrophy with a clinically normal heart. Patient aged 23.

no evident cardiac changes and where, from the possible presence of pulmonary tuberculosis, the expression of the first signs of cardiac hypertrophy would be expected on the right, this electrocardiographic

diagnosis seems questionable. Then at the same age, in a clinically normal heart there appear electrocardiographic changes of right ventricular hypertrophy.

W. J., a well built young man of 23, weighs 140 pounds. He was regarded as having a case of periodic paralysis. His cardiac dulness measured 4.5 cm. to the right and 9 cm. to the left of the median sternal line, with the apex in the fourth interspace, inside the nipple line. Blood-pressure and urinary findings were normal. Figure 5 shows his electrocardiogram.

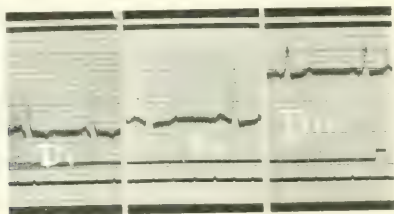


Fig. 6.—Normal electrocardiographic findings in a greatly hypertrophied heart which at post mortem was grossly much more marked on the left.

No further mention of the other eight cases need be made beyond the fact that they had clinically normal sized hearts with normal electrocardiograms.

Further discussion of the other decades emphasizes the absence of a standard, and suggests the conclusion that, while in youth the right ventricular hypertrophy type of electrocardiogram is a common one, as age increases the left ventricular type predominates. It is impossible to say that there may not actually be a true hypertrophy, but as there is no possible standard for the normal, how can the pathological be diagnosed, and of what use would be the electrocardiographic findings?

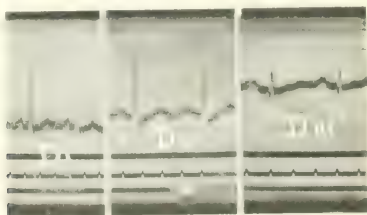


Fig. 7.—Normal electrocardiographic findings, where marked left ventricular changes would have been expected.

With this much information it will be interesting to review the electrocardiograms from a different angle—the comparison of all the

normal types of electrocardiograms with clinical findings, no matter what the cardiac condition. Sixty cases come under the broad conception of normal electrocardiograms—there was no progressive rise or fall in the size of the "R" waves. Of these, twenty-four would have been expected to be normal from the clinical findings, supplemented by the Roentgen ray. Twenty of the so-called normal electrocardiograms

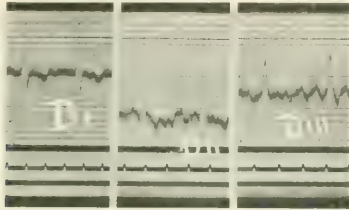


Fig. 8.—Normal sequence of derivations where right ventricular hypertrophy is suggested clinically. (Mitral stenosis).

were from cases that would, from clinical experience, have been regarded as definite instances of ventricular hypertrophy. Examples of this group seem advisable.

W. W., aged 49, a colored laborer of medium stature, weight 162 pounds, came into the hospital decompensated, and later died. The clinical diagnosis of myocardial insufficiency, aortic insufficiency, and arteriosclerosis was sub-

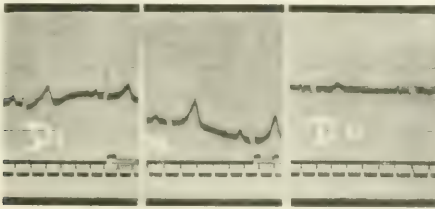


Fig. 9.—Normal electrocardiographic sequence in a case with lesions in both cardiac chambers.

stantiated at post mortem, and the heart, which had been greatly enlarged downward and outward with the apex in the sixth interspace, 12 cm. from the median sternal line, weighed 600 gm. There was marked dilatation and hypertrophy, especially of the left side, whose wall measured 2 cm. in thickness. There was right ventricular hypertrophy, but of an extent not to be compared with that of the left. The electrocardiogram, Figure 6, is that of a normal relation between the left and right ventricular potentials.

In the same way, A. B., a colored laborer, aged 60, was admitted and a diagnosis made of myocardial insufficiency, syphilis (Wassermann), arteriosclerosis, aortic insufficiency, dilated aortic arch. His apex was in the sixth

interspace and the precordial dullness extended 5 cm. to the right, and 13 to the left, which, for a man of 110 pounds, is a marked increase. His blood-pressure was 150 mm. and the urinary findings were normal. Surely it would be thought that this man had a marked left ventricular hypertrophy that was relatively much greater than any resulting right-sided enlargement. And yet, his electrocardiogram, Figure 7, was fairly normal in appearance.

Three of the cases which, clinically, should have been right-ventricular hypertrophy, showed normal electrocardiograms.

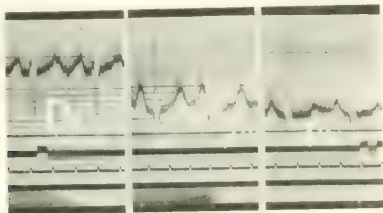


Fig. 10.—Electrocardiographic findings of right ventricular hypertrophy agreeing with the clinical findings.

T. H., a 45-year-old physician, showed typical signs of mitral stenosis and insufficiency, with symptoms of five years' duration following acute articular rheumatism. His apex was in the fourth interspace, 9 cm. from the median sternal line, with cardiac dullness extending to the right sternal border and 10.5 cm. to the left. The electrocardiogram (Fig. 8) shows, besides auricular fibrillation, a sequence of derivations associated with a normal relation between the two sides of the heart, in spite of the clinical findings which suggest right ventricular hypertrophy.

The remaining thirteen so-called normal electrocardiograms were obtained from patients with diseased hearts in whom, although it would have been expected that there would have been a predominating hypertrophy of one side or the other to give the electrocardiographic findings of hypertrophy, it is possible to conceive that there was a proportional hypertrophy of both sides to maintain a normal balance, and therefore a normal type of electrocardiogram.

F. S., aged 14, weighed 85 pounds, his cardiac symptoms were of eight years' duration, following an attack of acute articular rheumatism, and were diagnosed as resulting from mitral stenosis and insufficiency, with aortic insufficiency. Blood-pressure was 100, urine normal. The Roentgen ray showed a fairly normal sized heart. To percussion, the heart extended 5 cm. to the right, and 11.5 cm. to the left of the median sternal line, with the apex in the fifth interspace in the midclavicular line. His electrocardiogram (Fig. 9) was normal.

When one considers the tendency at this age to show normally a right ventricular sequence, and as this patient under normal conditions might have shown this sequence, it may be that in this normal sequence

we are dealing with an effort on the part of the electrocardiograph to express a pathological hypertrophy, a change from the normally found right-sided hypertrophy to the pathologically found normal sequence. Such hypotheses would seem to lead very far afield.

Among the collection of electrocardiograms, twenty-seven were found that suggested right ventricular hypertrophy. It would be advantageous to compare them with the clinical findings. Seven of these cases were clinically right-sided hypertrophy.

R. K., married, aged 28, weighing 94 pounds, with two years of cardiac symptoms, had a diagnosis made of pure mitral stenosis and exophthalmic goiter. To percussion, the heart measured 3.7 cm. and 11 cm. to the right and left of the median sternal line, with her apex in the left mammillary line. Blood-pressure was 85; urine, negative.

Probably this case was true right ventricular hypertrophy, and the electrocardiogram (Fig. 10) confirms this supposition. On the other hand, five cases of electrocardiographic right ventricular hypertrophy were found in patients with apparently normal hearts.

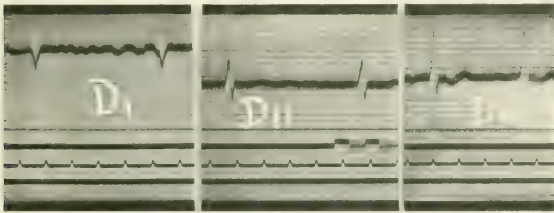


Fig. 11.—Electrocardiogram suggesting right ventricular hypertrophy in a clinical case of left ventricular hypertrophy.

It is striking to see four cases of electrocardiographic right-sided hypertrophy associated with clinical findings that point strongly to left-sided enlargement.

W. F., aged 51, weighing 124 pounds, was considered to have arteriosclerosis, myocardial insufficiency, aortic and mitral insufficiency. The Roentgen ray showed marked enlargement of the third curve on the left, signifying left ventricular enlargement. Blood-pressure was 100, urine showed chronic passive congestion changes. The patient came in badly decompensated and with auricular fibrillation. The heart, at the time of the electrocardiogram, measured 5.5 cm. to the right, and 14 to the left of the median sternal line. The apex was in the fifth interspace, three fingers' breadths outside of the nipple.

Quite possibly the patient did have a right ventricular hypertrophy, as the electrocardiogram (Fig. 11) showed, and as might be expected from the presence of decompensation. But if these electrocardiographic findings result from the preponderance of the right side, it is hard to believe that, with the Roentgen-ray and clinical findings, the

right side should have reacted more to the original lesion than did the left.

The eleven remaining cases could have been both left or right ventricular hypertrophy, from the clinical findings, and the question cannot be satisfactorily answered as to whether or not the right-sided hypertrophy relatively predominated. But, again, it is remarkable that the two sides should have hypertrophied so proportionately as to maintain the normal ratio as determined by an instrument so sensitive as to be of "great importance" in the diagnosis of the *earliest* changes on either side.

One hundred and twenty-five cases showed the sequence of derivations that has come to be associated with left ventricular hypertrophy. Many of these would have been expected from clinical findings.

S. R., aged 66, was admitted to the hospital badly decompensated six times with the diagnosis of arteriosclerosis, myocardial insufficiency, chronic nephritis and dilated aortic arch. Clinically his heart was greatly enlarged to the left and the electrocardiogram (Fig. 12) showed left ventricular hypertrophy, a condition substantiated at necropsy.

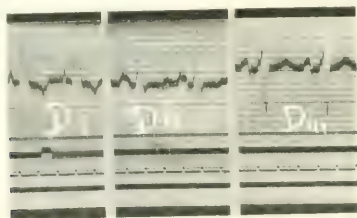


Fig. 12—Left ventricular hypertrophy according to the electrocardiogram, in spite of the time interval which would have permitted right sided hypertrophy of an extreme degree.

This case, which is quite similar to many others of this series, shows further that where there is a primary left-sided hypertrophy with seemingly right-sided dilatation and hypertrophy—even though of sufficient duration to allow the maximal response of the right side—that the right-sided hypertrophy does not necessarily surpass or equal the hypertrophy already on the left. So that in those cases of expected left ventricular hypertrophy where the electrocardiograms were of the normal sequence, it is not proved that the resulting right ventricular hypertrophy caused a balancing of the two sides to allow a normal electrocardiogram.

On the other hand, many of the cases which, according to the electrocardiogram, had left ventricular hypertrophy, showed clinically normal hearts. Realizing how indefinite is the standard in normal



people when there is no apparent cause for hypertrophy, it would seem of little avail to go into the different clinical histories. Of what importance is the knowledge of left ventricular hypertrophy in a clinically pathological case, if the same degree of left ventricular hypertrophy can be found in an apparently normal person? A further point develops from the perusal of these records. Patients with either recent or long-standing left ventricular hypertrophies did not show as typical a picture of left ventricular hypertrophy as did other patients with apparently normal hearts. Thus, several patients with hearts of normal dimensions from the Roentgen-ray and clinical findings had an inverted  $R_2$  and a very long negative  $R_3$ . Surely there can be no definite relationship between the degree of left ventricular hypertrophy and the degree of inversion of  $R_3$ .

Another view has been advanced as to the significance of the sequence of derivation. Professor Waller,<sup>1</sup> in several lectures and articles, has suggested that the increase of  $R_3$  has to do with a broad angle—the angle made by the electrical axis of the heart with the axis of the body. And he gives examples which show that where the heart is soft and flabby, and, according to the Roentgen ray, is more or less collapsed, mushroom-like over the diaphragm, the sequence of derivations corresponds to that which Einthoven<sup>2</sup> has associated with left ventricular hypertrophy. While Einthoven's right ventricular hypertrophy is to be connected with the heart that is nearly upright in the body and which is hard and firm, a review of the Roentgen-ray, electrocardiogram and post-mortem findings of this series does not substantiate Waller's conclusions. Thus, several cases with normal electrocardiograms showed, by Roentgen ray, hearts that were practically transverse and which seemed collapsed on the diaphragm. Other cases showed by Roentgen ray the normal position of the heart and right ventricular hypertrophy according to electrocardiogram. Again, one case showed a so-called upright heart with electrocardiographic findings of left ventricular hypertrophy. In this connection an interesting case can be cited: A patient from repeated Roentgen-ray and clinical examinations, was supposed to have dextrocardia. The electrocardiogram showed left ventricular hypertrophy, and was not that associated with transposition of the heart? Autopsy later showed a heart drawn over to the right by pulmonary conditions to the extent necessary to have simulated dextrocardia. The heart was upright in the body and was of fair consistency. This case would, did it substantiate Professor Waller's view, have undoubtedly shown right ventricular hypertrophy.

1. Waller: *Lancet*, London, 1913, p. 1436.

2. Einthoven: *Lancet*, London, 1912, i, 853.

Waller, and, following his lead, Pardee,<sup>3</sup> in a recent periodical, substantiate the fact that the electrical axis of the heart makes an angle with the body axis that is calculable easily enough from the different derivations. In no way, however, do they prove the coincidence of the anatomical and electrical axes of the heart, and a review of a number of cases suggests that they do not necessarily agree.

The literature on the electrocardiogram as applied to the diagnosis of cardiac hypertrophy is very confused. Hirschfelder,<sup>4</sup> in his last edition, in speaking of cardiac hypertrophy, says: "The electrocardiograms are, however, characteristic. In hypertrophy of the right ventricle, the R wave is normal or inverted in the first derivation ( $D_1$ ) and large in  $D_2$  and  $D_3$ . In hypertrophy of the left ventricle, the R wave is inverted in  $D_2$  and  $D_3$ ." In contradistinction to this dogmatic statement, James and Williams<sup>5</sup> conclude that it is difficult to explain the sequence of derivation obtained in the different types of electrocardiograms. "But the empirically determined fact that a downward deviated  $R_1$ , with an upward  $R_3$ , signifies right ventricular hypertrophy is of greatest clinical significance." They continue by saying that in left ventricular hypertrophy, the sequence of derivations is not so useful, because clinical findings are so easy. They seem to regard the electrocardiogram as diagnostic of cardiac hypertrophy.

L. Linitzky<sup>6</sup> says that in young people with low blood-pressure and with small hearts, the I or R wave is relatively small. And he goes on to speak of the effect of age, size of the heart and blood-pressure on the F or T wave.

Einthoven<sup>7</sup> associates right ventricular hypertrophy with a low  $R_1$  and high  $R_3$ , while he diagnoses left ventricular hypertrophy from a relatively low or inverted  $R_3$ . And his explanation necessitates the coincidence of the electrical and anatomical axes of the heart.

Lewis,<sup>8</sup> in the same way, gives the impression that there is a normal type of electrocardiogram and that deviations from this beyond the age of three months (at which time he states the infant's electrocardiogram changes from the right ventricular hypertrophy type to the normal) are of importance in the diagnosis of cardiac hypertrophy. He very wisely points out the difficulty that often exists in making the diagnosis of cardiac hypertrophy from a physical examination; but he perhaps rather exaggerates the difficulty in concluding that "signs which are

3. Pardee: Jour. Am. Med. Assn., 1914, lxii, 1311.

4. Hirschfelder: Diseases of the Heart and Aorta, Ed. 2, 1913.

5. James and Williams: Med. and Surg. Rep., Presbyterian Hos., 1912.

6. Linitzky: Ztschr. f. Exper. Path. u. Therap., 1911, ix, 669.

7. Einthoven: Arch. f. d. ges. Physiol., 1908, cxxii, 517.

8. Lewis: Brit. Med. Jour., 1912, i, 1423.

customarily employed at the bedside are of little real value in differentiating between right and left ventricular hypertrophy." Certainly the bedside examination is very helpful, and the stress laid on the individual sign "the epigastric pulsation in right ventricular hypertrophy," which Lewis concludes is useless, is a matter of clinical experience; for there are many who have always regarded that sign as of little import. It is the graduation of all the features of a case and their algebraic summation that leads to the clinical diagnosis.

From the pathological study of a series of nine cases, Lewis<sup>9</sup> notes that the clinical discrepancies in clinical and electrocardiographic findings disappear if the exact weights of the two sides of the heart are compared with the electrocardiograms. Such studies are of immense value in the scientific study of the electrocardiogram, but are of little avail in the application to the patient. Even if they are carried out in a sufficient number of cases to confirm the ability of the electrocardiogram to characterize left and right ventricular hypertrophy (a condition not yet obtained), there would be question as to the actual clinical use. It would be hard to say from the electrocardiogram whether the patient was suffering from a mild left-sided lesion with marked right-sided resultants, or whether the lesion was fundamentally a slight right-sided lesion with no trouble on the left side. Without the clinical findings, a diagnosis from the electrocardiogram would seem dangerous, and if the clinical findings differed from the laboratory findings the laboratory findings would have to be corrected. And in addition, there is always the question in a pathological case, "What would the electrocardiogram have shown had the patient been normal?"

As opposed to the views of the English and American observers, the German writers substantiate the opinions expressed in this paper. Hering<sup>10</sup> sums up their conclusions in believing that there is but little dependence to be placed in the electrocardiographic findings in the diagnosis of cardiac hypertrophy.

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With the few cases in this series it is suggested that there is a right ventricular hypertrophy type of electrocardiogram in normal children, which with increasing age gradually passes through the normal to the left ventricular hypertrophy sequence and that there are many exceptions. Attention is called to the absence of a normal cardiovascular system on which to standardize the electrocardiographic findings; especially as age develops, accompanying emphysematous or arteriosclerotic

9. Lewis: *Heart*, 1914, v. 367.

10. Hering: *Deutsch. med. Wchnschr.*, xxxviii, 2155.

changes appear in varying degrees. The lack of concordance between clinical and electrocardiographic findings is emphasized, and conclusions are pointed out that suggest that the electrocardiogram as it is now understood is of little practical value in the diagnosis of cardiac hypertrophy.

This work was done during the past year, while working in Dr. Thayer's service. It is a pleasure to acknowledge his supervision.

The physical findings were tabulated from the hospital histories of the medical clinic with the permission of Professor Barker.

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## THE DEAD SPACE IN MODERATE AND LARGE RESPIRATORY VENTILATION \*

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In a publication by one<sup>1</sup> of us, it was shown that in emphysematous patients (the minute volume and rate of respiration remaining the same) the concentration of carbon dioxid in the alveolar air increased when the degree of emphysema increased. It was also shown that this increased concentration of carbon dioxid in alveolar air was not caused by impairment of the function of external respiration, but was due to impairment of the ventilatory function of the lung. It was at first suspected that the dead space was increased in emphysema but when we collected the entire minute volume of air in a large rubber bag and took samples of alveolar air during the collection of the minute volume of air, we found that the dead space in patients who had severe emphysema was no larger than in normal persons. A large rubber bag 20 inches square was used for the purpose. The bag contains 60 liters of air before the tension of its walls will offer an appreciable resistance to expiration. Near the mouthpiece a lateral opening in the tube is provided for taking specimens of alveolar air.

The tube leading to the bag has a capacity of 120 c.c., so by clamping the tube near the bag and having the patient stop the end of the mouthpiece at the end of an expiration we could procure samples of alveolar air while the minute volume of air was collecting. The collected air was then passed through a meter and specimens of the expired air were taken for analysis while the air was measured with the meter.

The patient, S. G., had severe emphysema without asthma. Cyanosis was very pronounced.

Resp. rate = 20.5 per min.

Min. vol. = 8,200 c.c.

Expired air contained 4.38 per cent. of CO<sub>2</sub>.

\* Submitted for publication Oct. 1, 1914.

1. Hoover, C. F.: The Minute Volume and Alveolar Air in Pulmonary Emphysema, *THE ARCHIVES INT. MED.*, 1913, xi, 52.

Three specimens of alveolar air contained 7.49 per cent., 7.86 per cent. and 7.00 per cent. of  $\text{CO}_2$ .

The mean  $\text{CO}_2$  content of alveolar air = 7.45 per cent.

Each respiration = 400 c.c.

The alv. air = 235 c.c.

The dead space = 165 c.c.

Another test of S. G.'s respiration made in the same manner as above gave the following results:

Time of collection = 2 minutes.

No. of resp = 45.

Total expiration = 22,500 c.c.

Min. vol. = 11,250 c.c.

Each respiration = 500 c.c.

$\text{CO}_2$  in two specimens of alveolar air = 7.17 per cent. and 7.44 per cent.

$\text{CO}_2$  in expired air. Two specimens = 4.74 per cent. and 4.61 per cent.

Mean  $\text{CO}_2$  for alveolar air = 7.30 per cent.

Mean  $\text{CO}_2$  for expired air = 4.67 per cent.

Alv. air in each resp. = 319 c.c.

Dead space = 181 c.c.

Alveolar air = 63 per cent. of the min. vol.

On another trial when S. G. breathed 434 c.c. each respiration, the alveolar air contained 7.80 per cent. carbon dioxide and the total expired air contained 5.02 per cent. carbon dioxide. The dead space amounted to 155 c.c.

On all these occasions S. G. was cyanotic but suffered no sense of air hunger. When S. G. exercised we found the carbon dioxide content of his alveolar air was elevated so promptly and his ventilatory capacity was so limited that the dead space was not increased. When the estimates were made in the same manner employed by Haldane and Douglas, S. G. could increase his ventilation only by increasing the rate of respiration. He had no reserve expansion of the lungs which would increase the volume of each respiration; consequently his dead space remained unchanged with exercise, but the alveolar air carbon dioxide increased as much as 1.5 per cent. with moderate exercise. This increase of carbon dioxide percentage in his alveolar air permitted only very moderate walking. Severe exercise was unendurable.

Dr. G., a perfectly healthy young man, 5 ft. 8 in. high and weighing 140 pounds, breathed tranquilly while seated.

Time = 2 min. 2 sec.

No. of resp. = 29.

Total exp. = 25,750 c.c.

Each resp. = 887 c.c.

$\text{CO}_2$  in alveolar air  $\left\{ \begin{array}{l} \text{No. 1} = 5.33 \text{ per cent.} \\ \text{No. 2} = 4.91 \text{ per cent.} \\ \text{No. 3} = 4.78 \text{ per cent.} \end{array} \right\}$  Mean = 5.00 per cent.

Expired air in  $\text{CO}_2$   $\left\{ \begin{array}{l} \text{No. 1} = 4.00 \text{ per cent.} \\ \text{No. 2} = 4.10 \text{ per cent.} \end{array} \right\}$

Using mean alveolar air  $\text{CO}_2$  of 5.00 per cent. and 4.10 per cent.  $\text{CO}_2$  for the total expired air.

The alveolar air = 81 per cent. of the minute volume.

The dead space = 160 c.c.

Alveolar air of each resp. = 72 per cent.



Dr. G.'s dead space was measured many times while breathing tranquilly when seated and it was always found to measure between 150 and 180 c.c. We then made a series of experiments on Dr. G. and Dr. H. after the method employed by Haldane and Douglas and found the dead space increased as the volume of each respiration increased with exercise. We found, however, that with exercise the variations of carbon dioxid concentrations in our alveolar air were sufficient to give large variations in the estimated dead space when we were dealing with such large amounts for each respiration. We then suspected exercise had nothing to do with the large dead space but that the dead space enlarged because a large respiratory volume was not effective in diluting the alveolar carbon dioxid in direct proportion to the increasing volume of each respiration. Dr. G. breathed as deeply as possible five times and then began collecting the expired air.

Breathed 15 times in 1 minute and 40 seconds.

Total expired air = 48,880 c.c.

Each respiration = 3,258 c.c.

CO<sub>2</sub> in alveolar air { No. 1 = 3.59 per cent.  
No. 2 = 3.69 per cent.  
No. 3 = 3.47 per cent. } Mean = 3.58 per cent.

CO<sub>2</sub> in expired air { No. 1 = 2.87 per cent.  
No. 2 = 2.93 per cent. } Mean = 2.90 per cent.

Alveolar air in each respiration = 2,666 c.c.

Dead space = 592 c.c.

Then in order that forced breathing should be avoided, Dr. G. breathed very slowly but very deeply. It was found that a deep respiration taken every 20 seconds was just sufficient to maintain respiratory comfort.

Dr. G. Breathed 5 minutes.

One respiration every 20 seconds.

Total respirations = 15.

Total expired air = 50,370 c.c.

Each respiration = 3,351 c.c.

CO<sub>2</sub> in alveolar air { No. 1 = 4.19 per cent.  
No. 2 = 4.05 per cent. } Mean = 4.12 per cent.

Expired air CO<sub>2</sub> { No. 1 = 3.18 per cent.  
No. 2 = 3.04 per cent.  
No. 3 = 3.09 per cent. } Mean = 3.10 per cent.

Alveolar air in each respiration = 2,521 c.c.

Dead space = 830 c.c.

The same experiment repeated gave the following:

Time of collection = 5 minutes.

No. of respirations = 15.

Total expired air = 52,000 c.c.

Each respiration = 3,406 c.c.

CO<sub>2</sub> in alveolar air { No. 1 = 4.09 per cent.  
No. 2 = 4.32 per cent. } Mean per cent. = 4.20.

CO<sub>2</sub> in expired air { No. 1 = 3.24 per cent.  
No. 2 = 3.29 per cent. } Mean = 3.26 per cent.

Alveolar air in each respiration = 2,643 c.c.

Dead space = 763 c.c.

We then wished to see how the dead space would measure when Dr. G. breathed tranquilly but employed an excursion of the thorax which was just short of conscious effort. At this period of our research we were still of the opinion that a forced inspiratory effort dilated the bronchial tree after the infundibula were dilated. We suspected that the point of transition from tranquil breathing to conscious effort in lifting the thoracic cage would mark the point where the dead space increased.

Feb. 22, 1914, Dr. G. breathed tranquilly while seated. The breathing was just sufficiently deep so that he was not conscious of any effort at inspiration or expiration. Dr. G. said it was the upper limit of tranquil excursion, and larger inspiration would have required a conscious effort. After he had breathed in this manner for one minute, the collection of air was commenced.

Time of collection = 3 minutes.  
 Total expired air = 59,800 c.c.  
 No. of respirations = 46.  
 Each respiration = 1,300 c.c.  
 Min. vol. = 19,933 c.c.

Specimens of alveolar air were taken at the end of the first, second and third minutes.

CO<sub>2</sub> in alveolar air { No. 1 = 3.40 per cent.  
                               No. 2 = 3.20 per cent.  
                               No. 3 = 3.23 per cent. } Mean = 3.27 per cent.  
 CO<sub>2</sub> in expired air { No. 1 = 2.89 per cent.  
                               No. 2 = 2.97 per cent.  
                               No. 3 = 2.88 per cent. } Mean = 2.91 per cent.

Alveolar air in each respiration = 1,155 c.c.  
 Dead space = 145 c.c.

Feb. 26, 1914, Dr. G. breathed for one minute fifteen times with slightly conscious effort of expansion. Then the collection of air commenced.

Dr. G. Breathed every 5 seconds for 2 minutes, 5 seconds.  
 The total expiration = 52,500 c.c.  
 Each respiration = 1,810 c.c.

Specimens of alveolar air were taken 30 seconds apart.

CO<sub>2</sub> of alveolar air { No. 1 = 3.75 per cent.  
                               No. 2 = 3.37 per cent.  
                               No. 3 = 3.07 per cent.  
                               No. 4 = 3.29 per cent. } Mean = 3.37 per cent.  
 CO<sub>2</sub> in expired air { No. 1 = 3.04 per cent.  
                               No. 2 = 2.94 per cent. } Mean = 2.97 per cent.  
 Alveolar air in each respiration = 1,594 c.c.  
 Dead space = 206 c.c.

March 6, 1914, Dr. G. breathed deeply for one minute and then the collection of air was begun. Dr. G. breathed every ten seconds for three minutes. The expirations and inspirations were made as rapidly as possible. During the interim in which the breath was held, Dr. G.

held the glottis closed, so that from the end of a forced expiration until the beginning of the succeeding inspiration there could be no escape of carbon dioxide from the lungs.

	Time of collection = 3 minutes.	
	No. of respirations = 18.	
	Total expired air = 5,760 c.c.	
	Each respiration = 3.202 c.c.	
CO <sub>2</sub> in alveolar air	$\left\{ \begin{array}{l} \text{No. 1} = 3.67 \text{ per cent.} \\ \text{No. 2} = 3.30 \text{ per cent.} \\ \text{No. 3} = 3.39 \text{ per cent.} \end{array} \right.$	Mean = 3.45 per cent.
CO <sub>2</sub> in expired air	$\left\{ \begin{array}{l} \text{No. 1} = 2.61 \text{ per cent.} \\ \text{No. 2} = 2.65 \text{ per cent.} \end{array} \right.$	Mean = 2.63 per cent.
Alveolar air in each respiration	= 2,440 c.c.	
Dead space	= 762 c.c.	

On account of the varying percentages of carbon dioxide in the alveolar air we concluded to estimate the dead space by collecting the expired air of a single respiration and then compare the carbon dioxide content of the expired air with the carbon dioxide content of the end expiratory air of the same expiration.

For this purpose we used an 8-inch rubber bag. The bag contains 4 liters of air without offering any appreciable resistance to expiration.

A rubber tube leading to the bag contained 1 c.c. of water for every centimeter in length. The capacity of the tube measured with water was 120 c.c. A lateral opening in the mouthpiece enabled us to take samples of the end expiration air by clamping the tube at the bag and stopping the end of the mouthpiece at the end of a quick forced expiration. The results obtained by this method were quite the same as those procured by using the large bag. The larger the volume of respiration the larger the dead space found. This, however, did not settle the question, although it was growing more apparent that the great increase of the dead space in deep inspirations was an absurdity.

We then sought evidence of the comparative values of moderate and increasingly large respirations for dilution of the residual air in the lungs.

First, we wished to determine whether the amount of residual air was constant at the end of a forced expiration. When Dr. G. was seated he first made a forced expiratory effort and immediately followed the forced expiration with a forced inspiration. In each trial the expiratory effort was a maximum effort. The expired air from the maximum inspiration was captured in the small rubber bag and then measured by passing it through a meter. We found in many trials that the amount of air was very constant and varied only 200 c.c. The amounts measured always ranged between 3,600 c.c. and 3,800 c.c. This being the case, we are then justified in saying that in a normal person the amount of residual air in the pulmonary system at the

end of a forced expiration will be constant. Starting, then, with a constant residual air and employing a constant time for the initial expiration, a constant time for the inspiration and a constant time for the second expiratory effort, we have a method for measuring the dilution of the carbon dioxid in the residual air with varying inspiratory volumes. We first determined how much carbon dioxid per minute was being excreted.

April 17, 1914, two estimates were made. The first was made one hour after a full meal of proteins and carbohydrates, and the second estimate was made four hours after the meal. The specimens were procured by breathing into the large bag for five minutes while tranquilly seated. The two trials gave 417 c.c. of carbon dioxid moist per minute one hour after the meals. And the second trial four hours after the meal, gave a carbon dioxid excretion of 430 c.c. per minute. The lesser amount was employed, as that result was obtained shortly before the following experiments were made. We then started with the estimate of a carbon dioxid excretion of 6.95 c.c. per second. Dr. G. then made a forced expiration after breathing tranquilly for a few minutes while seated. This expiration was made through a tube 2 meters long fitted with a lateral opening in the mouthpiece so that a specimen of the end expiration air could be taken.

Then an inspiration was taken lasting two seconds. This was followed by a forced expiration lasting two seconds. The second expiration was made into the small bag fitted with a tube and mouthpiece which had a capacity of 120 c.c. At the end of the expiratory effort the tube was clamped at its junction with the bag and Dr. G. stopped the opening of the mouthpiece at the same instant. In this manner the end expiratory air of the second expiration was sampled and the total expired air was then thoroughly mixed by churning the bag and samples of the total expired air were taken from the lateral opening in the mouthpiece while the air was being passed through a meter. Knowing the exact dilution of the expired air with atmospheric air in the tube leading to the bag, we can accurately determine the carbon dioxid of the total expired air by estimating the carbon dioxid in the air contained in the bag.

We have then the following facts:

The excretion of carbon dioxid per second.

The carbon dioxid content of the residual air in the alveolar and dead space before ventilation.

The amount of ventilation.

The carbon dioxid in the expired air.

The carbon dioxid in the alveolar and dead space at the end of ventilation.

The time during that part of the procedure during which the excreted carbon dioxide was being contributed to the total expired air which was captured and its carbon dioxide determined.

The following are the results:

CO<sub>2</sub> excreted per second = 6.95 c.c.  
 Expired 1 second; alveolar air CO<sub>2</sub> = 6.06 per cent.  
 Inspired 2 seconds.  
 Expired 2 seconds; alveolar air CO<sub>2</sub> = 5.80 per cent.  
 CO<sub>2</sub> in expired air = 4.88 per cent.  
 Total expired air = 875 c.c.  
 Total alveolar air = 735 c.c.  
 Dead space = 140 c.c.

During the four seconds of inspiration and expiration 27.8 c.c. of carbon dioxide were contributed to the expired air.

We may assume the residual air of the lung to be 2,000 c.c., which is certainly a liberal estimate.

The dead space estimated in the experiment was 140 c.c. and as the volume of the respiration was very moderate we may assume the dead space unchanged during the experiment.

At the end of the first expiratory effort the total carbon dioxide in the pulmonary system can be expressed by the formula  $(2,000 + 140) 6.06$  per cent.

If we assume there were no carbon dioxide excreted during the following four seconds, then the carbon dioxide content of the alveolar and dead spaces at the end of the inspiratory effort may be expressed by  $2,000 + (875 - 140)$  multiplied by  $x$ . We then have the formula:

$$\frac{2140 \times 6.06\%}{2735} = x \text{ or } 4.74\%$$

This is the percentage of carbon dioxide we should have obtained in the alveolar air at the end of the second expiration had no carbon dioxide been excreted in the interim of four seconds. But 27.8 c.c. of carbon dioxide were contributed to the air in the infundibula and alveolar spaces. In this instance that amount of air equaled 2,735 c.c.

$$27.8 = 1.01\% \text{ of } 2,735$$

Therefore to the theoretically ventilatory result of 4.74 per cent. carbon dioxide we add the contributed carbon dioxide amounting to 1.01 per cent., and this amounts to 5.75 per cent., whereas the actual estimate made was 5.80 per cent.

Therefore in moderate respiratory amounts the dilution of the residual air carbon dioxide can be completely accounted for.

How is the dilution of residual air when large respiratory amounts are employed?

About two hours after the foregoing experiment was performed Dr. G. performed the following experiment:

Expired 1 second the alveolar air  $\text{CO}_2 = 6.23$  per cent.  
 Inspired 3 seconds.  
 Expired 2 seconds alveolar air  $\text{CO}_2 = 5.09$  per cent.  
 Amount expired air = 2,810 c.c.  
 $\text{CO}_2$  in expired air = 4.12 per cent.  
 Total alveolar air = 2,274 c.c.  
 Dead space = 536 c.c.

The total carbon dioxid content in the tracheobronchial and alveolar spaces at the end of the first expiration =  $(2,000 + 140)$  6.23 per cent.

If we accept the enlargement of the dead space to 536 c.c., as our results showed, then at the end of the deep inspiration the dilution of the carbon dioxid in the alveolar air is expressed by the formula:

$$2,000 + (2,810 - 536) \text{ times } x$$

From this we have the formula:

$$\frac{2,140 \times 6.23\%}{4,274} = x \text{ or } 3.11\% \text{ of } \text{CO}_2$$

This is the concentration of carbon dioxid in the alveolar air had there been no excretion of carbon dioxid during the respiration, which occupied five seconds.

Using the maximum amount of carbon dioxid found in the minute volume of air, namely: 430 c.c. during the five seconds 35.8 c.c. of carbon dioxid were excreted, which amounts to 0.83 per cent. of 4,274 c.c., which was the minimum amount of air in the alveolae and infundibula if we assume the deep inspiration enlarged the dead space. Therefore, adding 0.83 per cent. to 3.11 per cent., we have only 3.94 per cent., the amount of carbon dioxid we should have found in the alveolar air at the end of the deep respiration had the deep respiration been effective in proportion to the amount of the total inspiration. The concentration really found at the end of the deep respiration was 5.09 per cent. carbon dioxid. So the disparity between the actual and the theoretical dilution was 1.15 per cent. This can be accounted for only by the want of equal diffusion of gases in the infundibular and alveolar spaces when the lung is greatly distended.

Another method of treating the results algebraically shows how the effectiveness of dilution of the residual air diminishes with the increasing volume of respiration.

In our results the residual air is the only unknown factor. When treated in this manner we evolve the following formula:

First experiment, April 17.

Let  $x$  = the residual air in the alveolae.

Dead space = 140 c.c.

$\text{CO}_2$  concentration of alveolar air and dead space air at the end of the first expiration in Experiment 1 = 6.06 per cent.



$\text{CO}_2$  at the end of the first expiration =  $(x + 140)$  6.06 per cent. in the alveolae and dead space.

At the end of the inspiration the total  $\text{CO}_2$  in the alveolae =  $x + (875 - 140)$  times 5.80 per cent.

But 27.8 c.c. of  $\text{CO}_2$  are excreted during the four seconds, therefore

$$(x + 140) 6.06 \% + 27.8 = (x + 735) 5.80 \%$$

$$x 6.06 \% + 36.28 = x 5.80 \% + 42.63$$

$$(6.06 \% - 5.80 \%) x = 42.63 - 36.28$$

$$x = \frac{42.63 - 36.28}{6.06\% - 5.80\%}$$

$$x = \frac{6.06\% - 5.80\%}{5.83}$$

$$x = \frac{.0026}{.0026}$$

$x$  or residual air = 2,203 c.c., which is a very close estimate of the residual air.

If we employ the results of Experiment 2 of April 17 to estimate the residual air we will have the following formula:

$$x = \text{residual air.}$$

$$\text{CO}_2 \text{ secreted in 5 seconds} = 35.8 \text{ c.c.}$$

$$(x + 140) 6.23 \% + 35.8 = (x + 2,274) 5.09 \%$$

$$x 6.23 \% + (140 \times 6.23 \%) + 35.8 = x 5.09 \% + (2,274 \times 5.09 \%)$$

$$x 6.23 \% + 44.522 = x 5.09 \% + 115.7466$$

$$x 6.23 \% - x 5.09 \% = 115.746 - 44.522$$

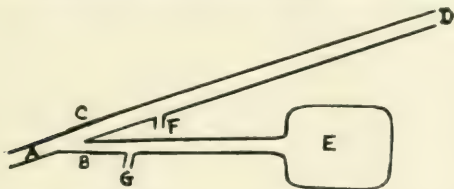
$$(6.23 \% - 5.09 \%) = 71.224$$

$$x = \frac{71.224}{0.0114}$$

$$x = \frac{71.224}{0.0114}$$

$$x \text{ or the residual air} = 6,274 \text{ c.c.}$$

This is of course absurd but should be true if the large ventilation diluted the residual air in proportion to the volume of ventilation.



In the figure A is a rubber tube which has the same lumen as its two branches B and C; E is a rubber bag with a capacity of 4,500 c.c.; F and G are lateral openings through which samples of the alveolar air may be procured.

April 25, an experiment was made to see what would be the actual effect of ventilation in a normal person when the dead space was artificially prolonged. The apparatus used consisted of the device illustrated in the accompanying figure.

Dr. G. breathed quietly while seated. After breathing for several minutes to obtain perfectly tranquil and comfortable ventilation, he then made a quick, forced expiration lasting one second. During this time a clamp was applied at B so all expired air passed through the tubes A, C, D. The tube C was 50 cm. longer than the tube B (which was 275 c.c. long), because at the end of the forced expiration (lasting one second) a sampling tube with a capacity of 50 c.c. was filled with

alveolar air. The rubber tubing had a capacity of 1 c.c. for each centimeter in length. Then, at the beginning of the inspiration, which was drawn through the tube A, C, D, the prolongation of the dead space was the same as the prolongation of the dead space for the following expiration, which was made through the tube B (with C clamped). At the end of the second expiration a sample of the alveolar air was taken at G. The expired air was captured in the bag F.

The following were the results of the experiment:

Expiration 1 second alveolar air  $\text{CO}_2$  = 6.26 per cent.  
Inspiration 3 seconds.  
Expiration 2 seconds alveolar air  $\text{CO}_2$  = 6.53 per cent.  
The expired air contained = 4.28 per cent.  $\text{CO}_2$   
Total alveolar air = 1,065 c.c.  
Dead space = 560 c.c.

We see when the dead space is actually prolonged 275 cm., a respiration of 1,625 c.c. was not sufficient to dilute the alveolar air, but resulted in a further concentration from 6.26 per cent. carbon dioxide to 6.53 per cent. carbon dioxide.

This result was confirmed by repetitions of the experiment and merely affords added proof against the dead space being enlarged with an increased volume of respiration.

The results of our studies of lung ventilation are quite consistent with Oppel's studies of the functional anatomy of the lung. Keith,<sup>2</sup> quoting Oppel, says:

If out of the rubber balloon a model of the terminal bronchiole infundibulum and alveoli be made and inflated, it is the central or infundibular space which expands most, the alveoli implanted on its walls being widened but at the same time rendered more shallow. The point which one seeks to emphasize is that it is not the alveoli but the infundibula that should be regarded as the essential expansile parts of the lung.

From these results it is quite apparent why we must employ such a large minute volume of air to lower the carbon dioxide concentration of the alveolar air in forced breathing.

This conception also explains the respiratory limitations in physical exercise.

It is also a protective measure for maintaining a constant concentration of carbon dioxide at the respiratory membrane.

Thus far we have always spoken of ventilation of the lung as a process in which the alveolar air is diluted by the tidal air. This is true in one sense, but we have lost sight of another view of lung ventilation which the foregoing experiments strongly suggest. Lung ventilation amounts to concentration of the carbon dioxide of alveolar air into the bubble of tidal air which enters the atrium with each

2. Hill: Further Advances in Physiology, p. 186.

inspiration. Ventilation also means a concentration of the oxygen of the tidal air into the alveolar air.

When we take this view of the lung ventilation it is apparent why ventilation of a lobule with a large bubble of air does not secure a diminution of the carbon dioxid concentration in the alveolar air proportionate to the volume of ventilation. Our results prove that when from 700 to 1,300 c.c. are inspired, there is a concentration of carbon dioxid in the inspired air which equals that of the air at the respiratory membrane or at least so nearly so that our methods enable us to account for the effectiveness of a known volume of ventilation in diluting the alveolar air carbon dioxid when these moderate amounts of ventilation are employed. But when large amounts of air are employed (for instance, 3,600 c.c.), then the bubble of air in the atrium is too large to procure a concentration of carbon dioxid in the bubble of ventilating air which will equal or nearly equal the concentration of carbon dioxid that exists at the respiratory membrane. The reason for this seems to lie in the fact that there is not sufficient time for this to be accomplished. The act of respiration is continuous. The transition from the inspiratory to the expiratory phase occurs in so brief a time that when the ventilating bubble is of considerable size there is not sufficient time to procure a uniform concentration of carbon dioxid in all the air contained in a lobule of the lung. With this idea in mind we made further experiments to see what effect the arrest of respiration at the end of an inspiration would have on the size of the dead space and on the concentration of carbon dioxid in the alveolar air.

Dr. G. breathed tranquilly (while seated) into the large rubber bag.

Time of collection = 5 minutes.  
Total expiration = 66.650 c.c.  
CO<sub>2</sub> in expired air = 4.10 per cent.  
CO<sub>2</sub> per minute = 534.53 c.c.

Dr. G. breathed quietly and then at the end of a normal inspiration he made a forced expiration lasting one second. A specimen of alveolar air was taken at the end of this expiratory effort. Then G. took a moderate inspiration and held his breath with the glottis closed for ten seconds; then he expired two seconds and a specimen of alveolar air was taken at the end of this expiratory effort. The total expiration was also captured. There was then an interval of twelve seconds during which the excreted carbon dioxid was being concentrated in the alveolar air.

The following results were procured:

First alveolar air CO<sub>2</sub> = 5.75 per cent.  
Total expired air = 820 c.c.  
CO<sub>2</sub> in the expired air = 5.72 per cent.  
Second alveolar air CO<sub>2</sub> = 6.85 per cent.  
Total alveolar air = 684 c.c.  
Dead space = 136 c.c.

Applying the same formula we employed in former experiments.

$$\begin{aligned}(2,000 + 150) 5.75 \% &= (2,000 + 820 - 134) \times \\ 2,150 \times 5.75 \text{ per cent.} &= 2,684 \text{ times } x \\ x &= 4.60 \text{ per cent.}\end{aligned}$$

The amount of carbon dioxide in the alveolar air would have been 4.6 per cent. had there been no carbon dioxide excreted during the interval of twelve seconds. The amount of carbon dioxide given off in twelve seconds = 106.90 c.c. and  $106.90 = 3.98$  per cent. of 2,684. Therefore the concentration of carbon dioxide in the alveolar air would have been 4.60 per cent. + 3.98 per cent. = 8.58 per cent. if the carbon dioxide had not been stored in the blood. The amount of carbon dioxide found in the alveolar air at the end of the second expiration was 6.85 per cent. This experiment shows how promptly the carbon dioxide accumulates in the fluids of the body. It is true the dead space was small, but under the circumstance of arrested breathing we cannot assume that there was the same differentiation between alveolar air and dead space as in uninterrupted breathing. For this reason we cannot accept the estimate of the dead space as correct. We then tried holding the breath for thirty seconds with the following results:

Alveolar air end of expiration = 5.76 per cent.  $\text{CO}_2$ .  
Inspired and closed glottis for 30 seconds.  
Expiration 2 seconds alveolar air = 7.25 per cent.  $\text{CO}_2$ .  
Total expired air = 620 c.c.  
 $\text{CO}_2$  in expired air = 6.07 per cent.  
Total alveolar air = 510 c.c.  
Dead space = 110 c.c.

Employing the same formula we find the carbon dioxide concentration in the alveolar air we would have found had there been no carbon dioxide excreted during the interval of 32 seconds, was 4.93 per cent. Carbon dioxide excreted in 32 seconds = 284.80 c.c. and this amounts to 11.34 per cent. of 2,510 c.c. So we should have found 16.2 per cent. of carbon dioxide were the carbon dioxide not promptly stored in the fluids of the body as the percentage of carbon dioxide rises in the alveolar air.

On another occasion G. breathed tranquilly and we found he was exhaling 410 c.c. of carbon dioxide per minute.

A forced expiration lasting 1 second was made and the alveolar air contained 6.33 per cent. carbon dioxide.

G. inspired and held the glottis closed for 30 seconds.

Then G. expired 2 seconds.

The alveolar air  $\text{CO}_2$  = 7.33 per cent.  
Amount of expired air = 1,195 c.c.  
 $\text{CO}_2$  in expired air = 6.46 per cent.  
Total alveolar air = 1,053 c.c.  
Dead space = 142 c.c.

Therefore  $x = 4.44$  per cent. or the percentage of  $\text{CO}_2$  we would have found were there no  $\text{CO}_2$  excreted during the interim of 32 seconds.

But during this interim 218.56 c.c. of carbon dioxid were excreted and this amounts to 7.15 per cent. of 3,053. Therefore, were the carbon dioxid not promptly stored in the body fluids we would have obtained 11.59 per cent. carbon dioxid instead of 7.33 per cent. in the alveolar air.

#### SUMMARY

1. The optimum of respiratory volume is about 1,200 c.c. When the respiratory volume is increased beyond this amount the effectiveness of lung ventilation does not increase proportionately with the increased ventilation.

2. It is the want of diffusion of carbon dioxid in large respiratory excursions which has given rise to the error of supposing the dead space to be increased in exercise.

3. We have shown on the basis of measured ventilation and the results in diluting the residual air, that forced breathing is not effectual in ventilating the lungs in proportion to the increasing amounts of ventilating air. And conversely, when the amount of residual air is estimated on the basis of ventilatory results, the amount of residual air can be estimated with some accuracy when moderate amounts of air are inhaled, but when forced breathing is employed the residual air cannot be estimated from the measured results of ventilation.

4. When the dead space is artificially increased, the results of ventilation are not at all consistent with the ventilatory results which are ascribed by other investigators to an increase in the dead space in large respiratory excursions.

5. The inefficiency of large respiratory excursions contributes more to the limitations of endurance in exercise than do limitations in the circulatory system.

6. The foregoing results also prove the manner in which operative interference contributes to the relief of emphysema. Relief is not procured by diminishing the amount of residual air, whose carbon dioxid is diluted by respiration. Improvement is procured from the operation by restoring the ventilatory effectiveness of moderate respiratory volumes, the improvement from Freund's operation is due to diminution of the size of the lobules of the lung and not to changes in rigidity of the chest wall.

## THE OCCURRENCE OF NUCLEAR PARTICLES IN THE ERYTHROCYTES FOLLOWING SPLENECTOMY \*

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Recently O. Roth<sup>1</sup> reported unusual blood findings in a patient whose spleen had been removed twelve years before, because of supposed splenic anemia.† Numerically, the red corpuscles of Roth's patient varied between 5,600,000 and 6,468,000, the leukocytes between 8,900 and 16,000, while the hemoglobin fluctuated between 100 and 114 per cent. Thus, there was no anemia.

The microscopic examination of the fresh and stained specimens of blood revealed, as Roth points out, striking abnormalities. In the fresh specimen, it was evident that a large part of the erythrocytes presented one to two round, quite refractive inclusions. Generally, they were the size of a very small coccus, but at times the diameter amounted to one-sixth of that of the red cell. They moved slightly in the cell. When the blood was stained with Giemsa's mixture, it was seen that these bodies were structureless, sharply outlined and were stained red; they possessed all the characteristics of the Howell bodies. Usually one only, rarely two, bodies were observed in an erythrocyte. On one occasion Roth estimated that 20,000 red cells per 1 c.mm. contained nuclear particles or Howell's bodies.

Furthermore, in the stained blood, about one-half of the red corpuscles presented fine dots, which were stained blue with Giemsa's stain. The dots were usually single, though as many as three were found in a cell. Many of the cells containing a nuclear particle also contained dots.

Roth attributes the blood changes to the loss of the spleen.

In 1908, Schur<sup>2</sup> reported a similar case, in which he suspected the relationship between lessened splenic function and the occurrence of nuclear particles in the erythrocytes. His patient had had Basedow's

\* Submitted for publication Aug. 22, 1914.

† Presented before the American Society for the Advancement of Clinical Investigation, Washington, D. C., May, 1913.

1. Roth, O.: Ueber merkwürdige Erythrocyten-Einschlüsse bei einem Fall von Milzexstirpation, *Ztschr. f. klin. Med.*, 1912, lxxvi, 23.

† Roth is convinced that the patient was suffering from congenital hemolytic jaundice at the time of operation.

2. Schur, Heinrich: Ueber eigenartige basophile Einschlüsse in den roten Blutkörperchen bei einem Fall von abgelaufenem Morbus Basedowii mit nachfolgender schwerer makrocytischer Anämie. *Wien. med. Wchnschr.*, 1908, lvi, 442-511.



disease for ten years. She first consulted him in 1905; at this time the symptoms were mild. Blood examination showed 4,500,000 erythrocytes, 10,000 leukocytes, and 80 per cent. hemoglobin. In the fresh blood there was seen, in many of the red cells, a single refractive body, usually eccentric, and often moving in the cell. In the stained films these bodies were markedly basophilic. They were stained with all nuclear dyes, especially well with Giemsa's and with Romanowsky's stains. The bodies were least evident in preparations stained with Ehrlich's triacid stain, only a part of them staining green, while others were evident by a deeper staining at their periphery. The bodies were nearly always perfectly round; at times they appeared to be ring-like. There was never a definite structure to the bodies. At times their diameter amounted to one-fourth that of the red corpuscle. Generally, they were smaller, down to a minute point. The bodies were usually single; never more than two were found in a cell. Early in 1907 a severe anemia of the pernicious type developed, and in November the patient died. At autopsy the spleen was found to be 10 cm. long, 3 cm. wide at the upper end, only 1 cm. wide in its lower one-half. There was no thrombosis of the splenic vessels. Microscopically, the splenic pulp was found to be scanty; connective tissue predominated.

The peculiar inclusions in the erythrocytes, which were still present shortly before death, Schur identifies with the similar bodies observed by Howell<sup>3</sup> in the blood of the cat. In view of the severe anemia which developed, he looked on them as an expression of a degenerative change in the erythrocytes.

Schur believed the occurrence of the nuclear particles was in some way connected with the splenic atrophy, although, he says, extirpation of the spleen is not followed by marked changes in the erythrocytes, either in man or animals. He believed that the change in the spleen was not the primary factor, but that the atrophy of the spleen and the appearance of nuclear particles in the red cells were both probably due to some unknown toxin.

For some years I have been interested in the study of nuclear particles in the erythrocytes, especially their occurrence in human blood. In a previous report,<sup>4</sup> the blood of one patient whose spleen had been removed was noted. It was described (p. 95) in the following words:

In some bloods, however, single nuclear particles in the erythrocytes may be the main evidence of regeneration; this fact was well illustrated in the case of the patient following splenectomy, in whose blood, at one time (i. e.,

3. Howell, W. H.: *The Life-History of the Formed Elements of the Blood, Especially the Red Corpuscles*. Jour. Morphol., 1890, iv, 57.

4. Morris, R. S.: *Nuclear Particles in the Erythrocytes*, *THE ARCHIVES INT. MED.*, 1909, iii, 93.

thirteen days after splenectomy), thirty nuclear particles were found in about an hour and a half (examination with mechanical stage), while only one normoblast, no cells with basophilic granules, and a few with polychromatophilia were seen.

Roth's report led to a reexamination of the stained smears of the patient just referred to. The result of this, together with the findings in two other specimens of blood from splenectomized individuals, form the basis of the present report.

#### TECHNIC

All the bloods were stained with a Romanowsky stain (Giemsa's, Wilson's), as nuclear particles are best demonstrated in this way. The slides were examined with the  $\frac{1}{12}$ " oil immersion objective, ocular No. III (Leitz), a mechanical stage being employed. To narrow the field, a circular piece of paper, in the center of which a small square was cut, was inserted in the eye-piece. As nuclear particles are minute and are readily overlooked, it is essential, particularly when they are scarce, to move the stage very slowly, in order that all parts of the field may be carefully scrutinized.

CASE 1.—Patient of Dr. W. S. Thayer of Baltimore. The specimens, stained originally in November, 1908, with a Romanowsky stain, were faded. The cover slips were removed from the slide with xylol and in October, 1912, they were restained with Giemsa's stain (1 drop to 5 c.c. of water, allowed to act forty-eight hours). In a specimen obtained from the patient thirteen days after splenectomy, the red blood cells showed moderate anisocytosis and slight poikilocytosis. Many of the cells were pale. In counting 500 leukocytes, there were found 130 red corpuscles containing nuclear particles. Two cells were observed with two nuclear particles each, while one contained three; all the remaining cells presented only a single nuclear particle. The nuclear particles varied considerably in size and were almost always eccentrically situated in the cell. During the examination, three normoblasts and one erythrocyte containing basophilic granules were found. Chromatin dots (Weidenreich's *Chromatin-Stäubchen*) were fairly numerous but less so than the nuclear particles. The leukocytes were poorly differentiated. Blood platelets were apparently greatly increased in number and giant platelets were not uncommon.

In a smear from the same patient made three days later (i. e., sixteen days after splenectomy), only eighteen erythrocytes with nuclear particles were found; in all instances the nuclear particle was single and usually eccentrically situated. No erythroblasts were seen and only two cells with basophilic granules were encountered. Chromatin dots were much more numerous. A considerable percentage of the erythrocytes contained them. Their number varied from one to three in a cell; they were usually placed near the periphery of the corpuscle. They were stained reddish purple, like nuclei and nuclear particles. A differential count in this specimen (500 cells) gave: lymphocytes, 10.4 per cent.; large mononuclears and transitionals, 16 per cent.; polynuclear neutrophils, 64.4 per cent.; eosinophils, 7.6 per cent.; mast cells, 1.6 per cent.<sup>5</sup>

CASE 2.—Patient of Dr. Vilray P. Blair of St. Louis. A splenectomy was performed Nov. 15, 1912. Death occurred five days later. Smears of the

5. As blood counts were not made on the days that smears were prepared in this or the following cases, it is impossible to estimate, with any degree of accuracy, the number of cells per c.mm. containing nuclear particles.

patient's blood were made a few hours before death. The specimens were stained with Wilson's stain. Examination revealed ten erythrocytes with nuclear particles in counting 250 leukocytes. Most of the nuclear particles were of good size. During the examination one normoblast containing basophilic granules was seen. There was slight polychromasia, and a few cells contained chromatin dots.

CASE 3.—A specimen of blood from a patient a few days after splenectomy, was received from Dr. S. R. Miller of Baltimore. In counting 200 leukocytes, thirty-eight erythrocytes containing nuclear particles were observed, all single and of fair size. No normoblasts or cells with basophilic granules were found, nor was there polychromasia, anisocytosis or poikilocytosis.

My three cases with Roth's make four in whose blood nuclear particles have been found following splenectomy. In Schur's case, the great abundance of the nuclear particles with the marked splenic atrophy found at autopsy is suggestive of a causal relationship, in the light of the similar blood findings in Roth's case. In Roth's patient the nuclear particles were abundant years after splenectomy; in all of my cases the nuclear particles, though much less numerous, had appeared within two weeks after operation—in one case, indeed, within five days. It is unfortunate that we do not know whether nuclear particles were present or absent in the blood before operation.

Musser<sup>6</sup> reviewed the blood findings in man following splenectomy as reported in the literature. In no case does he mention the occurrence of nuclear particles. In the blood of three splenectomized dogs, he also makes no mention of nuclear particles.

The relationship between the occurrence of nuclear particles in the erythrocytes and complete (or partial) loss of splenic function, if such there be, remains to be demonstrated. The results in my three cases and in Roth's are suggestive. It is quite possible that it may be found that this is a characteristic blood change following removal of the spleen: for, unless one's attention were directed to them, it would be difficult to detect scattered nuclear particles in the course of the usual examination. It is, of course, not suggested that the finding of nuclear particles in the erythrocytes means absence of splenic function, for nuclear particles are not uncommon in various diseases of the blood.

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6. Musser, Jr., J. H.: An Experimental Study of the Changes in the Blood Following Splenectomy, *THE ARCHIVES INT. MED.*, 1912, ix, 592.

## AGE INCIDENCE IN SARCOMA\*

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In a previous statistical study<sup>1</sup> it was shown that the incidence of carcinoma is greatest at the age period 58 to 62, and that there is a definite decrease in carcinoma incidence after this period. In the present report it is proposed to treat by a similar method a large group of sarcoma ages obtained from the same source, hoping in this way to contribute to the knowledge of the biologic relationship between the two types of malignant disease.

In the past it has been the custom of both pathologists and surgeons to find in age incidence one of the chief points of difference between carcinomas and sarcomas. The usual statement of text-books has been that carcinoma is a disease of the old and sarcoma of the young. Da Costa<sup>2</sup> says that sarcomas may arise at any period from birth to extreme senility, but that they are commonest during youth and early middle age. On the other hand, Williams several years ago,<sup>3</sup> and again more recently,<sup>4</sup> has declared that this differentiation between carcinoma and sarcoma cannot be made. His conclusions are quoted in full:

The sarcomata may arise at any period of life; a certain number of cases are congenital; more are met with in early infancy, especially during the first five years, than at any other period prior to the twentieth year; after which sarcomata increase in frequency until middle life, becoming rarer again in old age.

It will be gathered from what I have stated that there are close analogies between the two diseases—sarcoma and carcinoma—such differences as are noticeable being due to diversity of origin and its consequences, rather than to any essential difference in the nature of the morbid process.

Williams found that he could derive the same conclusion either from the onset ages as taken from hospital records or from mortality returns.

As will be seen, our analysis of 265 consecutive cases of sarcoma bears out these conclusions in practically every particular. The method which has been used is the same as that employed in the preparation of the previous report<sup>1</sup> on age incidence in carcinoma. Therefore, it

\* Submitted for publication Aug. 14, 1914.

\* From the Department of Pathology, University of Michigan.

1. Weller: Age Incidence in Carcinoma, *THE ARCHIVES INT. MED.*, Chicago, 1913, xii, 539-545.

2. DaCosta: *Modern Surgery*, 1910, p. 365.

3. Williams: *Twentieth Century Practice of Medicine*, 1898, xvii, 487.

4. Williams: *The Natural History of Cancer*, 1908, p. 323.

will not be necessary to repeat it in detail here. The material from which these figures were derived consists of the consecutive cases of sarcoma of known age diagnosed in the pathological laboratory of the University of Michigan between the years 1895 and 1913. The advantages which this material possesses over either cancer censuses or mortality returns may again be briefly outlined. These data are derived

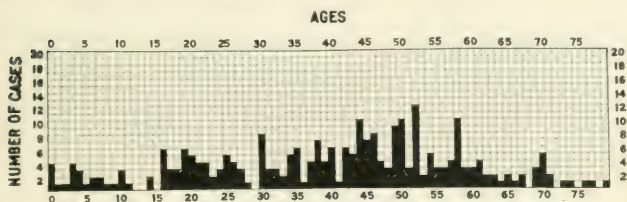


Chart 1.—Age distribution of sarcoma.

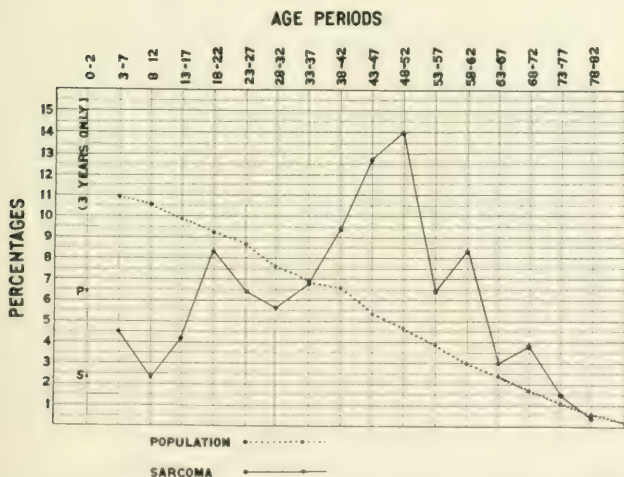


Chart 2.—Percentage of sarcoma cases for each age period contrasted with the percentage of total population living at each age period.

from a representative fraction of the population of Michigan and the neighboring states; the ages are given at an earlier stage of the disease than is possible in either of the other types of statistics; and each case has had complete microscopical verification. The figures for the age distribution of the total population are taken from the United States

Census Report<sup>5</sup> for 1900. Since less than 10 per cent. of these cases of sarcoma came from without the state of Michigan, it has been possible to use the age distribution of the population of Michigan alone without introducing any appreciable error.

The yearly distribution of the ages of the total 265 cases of sarcoma is shown by Chart 1. As was the case with a similar chart showing carcinoma ages, the years which are multiples of five, and also, in a lesser degree, the even years, are favored by patients in giving their ages. For instance, there are ten cases at age 50 and twelve at age 52, while only three patients gave 51 as their age and only two are found at 53. This error of approximate answers has been overcome almost entirely in all subsequent charts by the simple device of grouping all

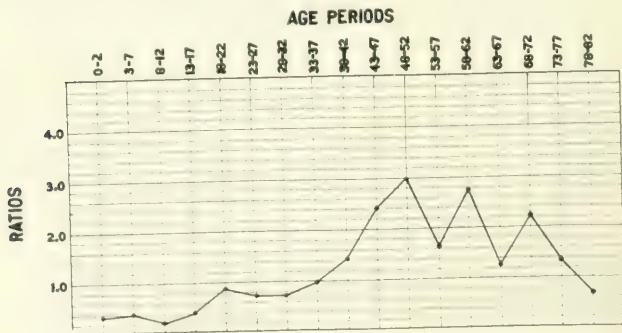


Chart 3.—Corrected curve of age incidence of sarcoma obtained by plotting a series of ratios between the percentages used in Chart 2.

figures in age periods of five years each with the multiple of five as the middle year in each group. From Chart 1 it should be noted that the number of cases of sarcoma is comparatively small until age 16 is reached, and that the greatest number of cases in any one year falls at age 52.

In Chart 2 the percentage of the total number of sarcoma cases for each age period is graphically contrasted with the percentage of the total population which is living at each age period. The sarcoma curve lies below the population curve until age 35 is reached. It then remains above the population curve until extreme old age is reached, at which period the proportion of the population found to be living and the number of sarcoma cases alike become too small to permit of drawing

5. Report, Twelfth Census, U. S., 1900, ii, Part 2, p. 52.



trustworthy conclusions. Stated in another way, these curves indicate that up to age 35 the incidence of sarcoma is less than it would be were sarcoma uniformly distributed throughout the entire population; that at age 35, the point of crossing of the two curves, the incidence of sarcoma is the same as it would be were sarcoma uniformly distributed throughout the total population, and that after age 35 sarcoma is much more prevalent than a uniform distribution would lead one to expect. Now the curve of *carcinoma* percentages was found to cross the curve of population percentages at age 37, and thus there is found to be an almost exact coincidence of the points of crossing in the two types of malignant disease. This close analogy in respect to age distribution will be more completely demonstrated in another chart.

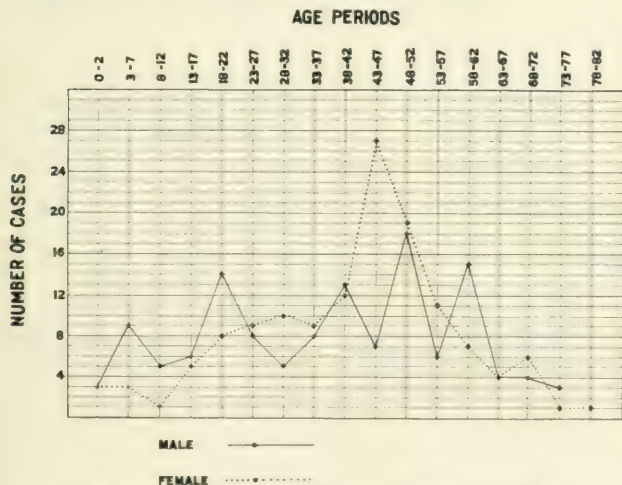


Chart 4.—Age distribution of sarcoma divided as to sex.

In Chart 3 the data embodied in Chart 2 are handled in a somewhat different way. The sarcoma curve of Chart 2 does not in itself give a true curve of age incidence for sarcoma, because of the decreasing population in each successive age period. In Chart 3 a corrected curve of age incidence is obtained by plotting a series of ratios between the percentages used in Chart 2. For instance, the

$$\text{Ratio for age period N} = \frac{\text{percentage of sarcoma for age period N}}{\text{percentage of population for age period N}}$$

From the true curve thus obtained it appears that the incidence of sarcoma is relatively low until the period of puberty is reached. At

that time there is a moderate increase, and this higher level is maintained until age 30. There is then a rapid rise until age period 48 to 52 is reached, at which point is found the maximum incidence of the disease. After this period the ratios again decrease until they become less than one in extreme old age. The fluctuations of this portion of the curve are due in part to the marked degree in which patients favored the multiples of ten in giving their ages, and in part to the smaller number of cases to be found at each age period, since with figures for the number of cases and for the population both relatively very small, slight variations cause correspondingly greater fluctuations in the curve.

If sarcoma were uniformly distributed in respect to age incidence, the ratio for each age period would be unity. This chart (No. 3) shows that the actual incidence is below this level throughout the first

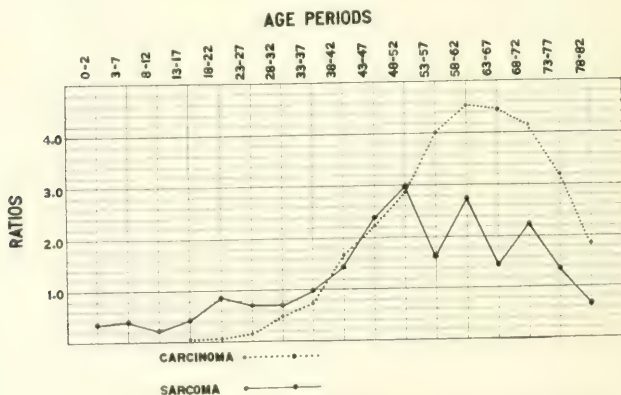


Chart 5.—Corrected curves of age incidence of carcinoma and sarcoma.

half of life and above unity throughout the second half of life. It is therefore, impossible to speak of sarcoma as a disease of the young. It is frequent in the young, but most common in late middle life.

In Chart 4 the age distribution of our sarcoma cases, divided as to sex, is shown. Of the total 265 cases, 129 occurred in males and 136 in females. When these are arranged according to age periods, there is a rough parallelism between the two curves. This would doubtless be more perfect if a larger number of cases were under consideration. The apex of the curve of cases in females is at age period 43 to 47. This is of interest for the apex of the curve of female carcinoma cases also occurred at this age period. Unlike carcinoma, however, these

curves do not definitely indicate any earlier incidence of sarcoma in females than in males. This was to have been expected, for in the previous report it was shown that the earlier cycle of carcinoma incidence in females is largely determined by the carcinomas of the breast and uterus, organs which early undergo involution changes. These two sources provided more than two-thirds of all our cases of carcinoma in women. In the anatomical distribution of sarcoma no such powerful factors are introduced.

On Chart 5 are plotted the fully corrected curves of age incidence of carcinoma and of sarcoma. The carcinoma curve is reproduced from the report to which reference has previously been made. The great similarity of the two curves is evident, but the most striking feature is the almost perfect coincidence of the two curves from age period 28 to 32 up through age period 48 to 52. Although the sarcoma incidence in the young is higher than the carcinoma incidence, it still remains less than unity, and so age incidence, instead of affording a means of contrast or differentiation, serves but to emphasize the biologic similarity between the two great types of malignancy.

In conclusion, the analysis here given indicates that:

1. The incidence of sarcoma is greatest at the age period 48 to 52. Therefore, sarcoma can no longer be considered a disease of the young.
2. After this period the sarcoma incidence gradually decreases.
3. There is no marked difference in the age distribution of sarcoma in males and in females.

4. Although in youth sarcoma incidence is somewhat higher than carcinoma incidence, there is throughout life a marked parallelism between the age incidence curves for the two types of malignancy, and for more than twenty years there is a practical coincidence, thus strongly suggesting that the causal or predisposing agencies in the two cases must either be identical or, at least, have much in common.

# STUDY XXIII. THE RELATION BETWEEN AMYLASE RETENTION AND EXCRETION AND NON-PROTEIN NITROGEN RETENTION IN EXPERIMENTAL URANIUM NEPHRITIS \*

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Tests for renal function fall into three general groups depending on: (1) The ability of the kidney to excrete from the circulation abnormal substances, such as dyes or drugs which are introduced into it; (2) analysis of the products of metabolism retained in the blood as a result of faulty eliminative powers of the kidney; (3) abnormalities in the physical and chemical properties of the urine.

The phenolsulphonephthalein test is an excellent example of the first group. Rowntree and Geraghty<sup>1</sup> have found that the amount of this dye excreted in the urine after its intramuscular or intravenous injection varies almost in proportion to the degree of injury existing in the kidneys. This test is used so generally by clinical and experimental observers that its value in the study of the renal function can be accepted without further comment.

Of substances studied in the blood of nephritics the concentration of the non-protein nitrogen and urea is of most importance. Among others Ascoli,<sup>2</sup> Strauss,<sup>3</sup> Obermayer and Popper,<sup>4</sup> Widal<sup>5</sup> and Foster<sup>6</sup>

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\* From the Laboratory of the Theory and Practice of Physic, Harvard Medical School, and the Medical Clinic of the Peter Bent Brigham Hospital.

\* This is one of a series of studies on experimental cardiorenal disease: Study I, Smith: Boston Med. and Surg. Jour., 1908, clviii, 696; Study II, Christian: Boston Med. and Surg. Jour., 1908, cliv, 8; Study III, Christian: Jour. Am. Med. Assn., 1909, liii, 1792; Studies IV-XV, Christian, Smith and Walker: THE ARCHIVES INT. MED., 1911, viii, 468-551; Study XVI, Christian and O'Hare: THE ARCHIVES INT. MED., 1913, xi, 517; Studies XVII and XVIII, O'Hare: THE ARCHIVES INT. MED., 1913, xii, 49, 61; Study XIX, Christian and O'Hare: Jour. Med. Research, 1913, xxviii, 227; Study XX, Walker and Dawson: THE ARCHIVES INT. MED., 1913, xii, 171; Study XXI, Fitz: THE ARCHIVES INT. MED., 1914, xiii, 945; Study XXII, Christian: THE ARCHIVES INT. MED., 1914, xiv, 827.

1. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1910, i, 579; THE ARCHIVES INT. MED., 1912, ix, 284.

2. Ascoli: Pflüger's Arch. f. d. ges. Physiol., 1901, lxxxvii, 103.

3. Strauss: Die Chronische Nierentzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung., Hirschwald, Berlin, 1902.

4. Obermayer and Popper: Ztschr. f. klin. Med., 1909, lxxvii, 332.

5. Widal: Bull. et mém. Soc. méd. d. hôp., Paris, Series 3, 1911, xxxii, 627.

6. Foster: THE ARCHIVES INT. MED., 1912, x, 414.

showed that in the majority of cases the nitrogen of the blood increases with an increasingly severe nephritis, and that the degree of accumulated blood nitrogen affords valuable information in regard to the prognosis.

Heretofore, urinalysis, except in relation to the output of chlorids, nitrogen and water, has contributed little to our understanding of renal function. In 1908, however, Wohlgemuth<sup>7</sup> began a series of studies with the starch-splitting ferment amylase (or diastase). He found that the amount of this enzyme which was excreted in the twenty-four hour urine of normal men varied within narrow limits and was almost constant for a given individual. In the urine of nephritics, on the other hand, the amount of the enzyme excreted in the urine diminished in proportion to the severity of the disease. Wohlgemuth, therefore, suggested that the determination of amylase in urine afforded a valuable clinical test for renal function.

His results with this test have been confirmed both by experiments and by clinical studies. Hirata<sup>8</sup> showed that in rabbits, as well as in man, the twenty-four hour urine and the blood serum contained normally a constant amount of amylase. When corrosive sublimate, uranium nitrate, or chromic acid nephritis was produced the amylase in the urine diminished, and accumulated in the blood in almost direct proportion to the severity of the existing lesions. Von Benczur,<sup>9</sup> Wynhausen,<sup>10</sup> Rosenthal,<sup>11</sup> Marino,<sup>12</sup> Corbett<sup>13</sup> and Geyelin<sup>14</sup> have observed the excretion of amylase in nephritis and have found that it diminishes as the severity of the disease increases. Therefore there is sufficient evidence to prove that of substances constantly found in urine the amylase excretion represents a reasonably accurate test for the renal function.

The desirability of correlating as many tests for renal function as possible to determine their true values has been self-evident and has been attempted both in animal experiments and clinical studies. Frothingham, Fitz, Folin and Denis<sup>15</sup> produced uranium nephritis in rabbits and followed the relation between the non-protein nitrogen retention in the blood and the excretion of phenolsulphonaphthalein in the urine. The two tests paralleled each other as indicators of

7. Wohlgemuth: Ueber eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments.

8. Hirata: *Biochem. Ztschr.*, 1910, xxviii, 23.

9. Von Benczur: *Wien. klin. Wchnschr.*, 1910, xxiii, 890.

10. Wynhausen: *Berl. klin. Wchnschr.*, 1910, xlvii, 2107.

11. Rosenthal: *Deutsch. med. Wchnschr.*, 1911, xxxvii, 923.

12. Marino: *Deutsch. Arch. f. klin. Med.*, 1911, ciii, 325.

13. Corbett: *Quart. Jour. Med.*, 1913, vi, 351.

14. Geyelin: *THE ARCHIVES INT. MED.*, 1914, xiii, 96.

15. Frothingham, Fitz, Folin and Denis: *THE ARCHIVES INT. MED.*, 1913, xii, 245.

renal function, but had one essential difference. The phenolsulphonephthalein excretion in the urine dropped rapidly to its lowest point and returned rapidly to normal with recovery of the kidney. The non-protein nitrogen of the blood accumulated more gradually and returned to normal more gradually. In other words, the phenolsulphonethalein test showed the renal function at the time the test was made, while the blood nitrogen was rather a measure of an accumulating difference between the amount of waste nitrogen produced in metabolism and the amount eliminated by the kidneys. Therefore in the latter test the duration of the disease was an important factor. Confirmatory results illustrating the close parallelism of these two tests have been obtained in clinical observations by Agnew<sup>16</sup> and by Frothingham and Smillie.<sup>17</sup>

Geyelin<sup>14</sup> compared the excretion of amylase with that of phenolsulphonephthalein in a series of cases of nephritis and found that the results of these tests were essentially similar. Geraghty, Rowntree and Cary<sup>18</sup> found that although the phenolsulphonephthalein test gave more accurate information as to the degree of one-sided lesions of the kidney than the amylase test, yet the latter gave findings which were parallel.

Thus it has been shown that on the whole the excretion of amylase varies as does that of phenolsulphonephthalein in nephritis, and that as the excretion of phenolsulphonephthalein diminishes, the non-protein nitrogen of the blood accumulates. It seemed important to compare the amylase excretion in the urine and the amylase accumulation in blood serum with the accumulation of non-protein nitrogen in the blood of animals with nephritis to make comparative studies between these three tests more complete.

Accordingly, acute nephritis was produced in rabbits by means of a single dose of uranium nitrate (from 2 to 10 mg.) given subcutaneously. Two series of experiments were made. In the first series the animals were injected with uranium nitrate and were killed (under anesthesia) by bleeding from the carotid arteries. They were killed on consecutive days from one to ten days after the uranium nitrate was administered in order to secure histological record of the pathological lesions in the kidney, and to determine their relation to the non-protein nitrogen in the blood, to the amylase in the blood, and to the amylase in the urine at different stages of the nephritis. In these experiments the amylase of the urine was estimated from day to day. The blood was analyzed only on the day the experiment was begun and on the day the animals were killed. The kidney tissues were preserved for

16. Agnew: *THE ARCHIVES INT. MED.*, 1914, xiii, 485.

17. Frothingham and Smillie: *THE ARCHIVES INT. MED.*, 1914, xiv, 541.

18. Geraghty, Rowntree and Cary: *Ann. Surg.*, 1913, lviii, 800.



the histological examination in Zenker's fluid and were stained with eosin and methylene blue.

In the second series of experiments, the nephritis was allowed to run its natural course. The non-protein nitrogen of the blood and the amylase of the urine were determined periodically. Amylase in the blood serum could not be estimated so often on account of the anemia induced from such frequent and relatively large bleedings.

The rabbits were kept in metabolism cages of moderate size. They were fed with carrots, oats and water. Each rabbit consumed about 100 gm. of carrot and 50 gm. of oats per day except for a few days at the height of the nephritis. In addition each rabbit was given 50 c.c. of water by stomach tube every morning to insure as constant an output of urine as possible.

The urine specimens from the metabolism cages were collected in receivers which contained 10 c.c. of toluol as a preservative. Every morning, the animals' bladders were emptied by massage and the urines so obtained were added to the containers to complete the twenty-four hour specimens.

The amylase readings in both urine and blood serum were made by the method of Wohlgemuth and Noguchi.<sup>19</sup> In brief, this depends on determining the amount of starch which is converted to dextrin or lower products by a known amount of urine or blood at a given temperature during a given interval of time. Iodin is used as an indicator of the starch digestion. Wohlgemuth has taken for a unit which he calls "d" the number of cubic centimeters of .1 per cent. soluble starch solution digested in one-half hour by 1 c.c. of urine or blood serum at a temperature of 38 C. "D" is the number of cubic centimeters of starch solution digested by the twenty-four hour urine. Rosenthal in obtaining the "absolute diastatic strength" of urine has preferred to divide Wohlgemuth's "D" reading by 2.

In the experiments with urine both "d" readings and the "absolute diastatic strength" were recorded to show the effect of dilution on the excretion of amylase. This question has been discussed by various observers. Wynhausen,<sup>10</sup> Corbett,<sup>13</sup> Rosenthal,<sup>11</sup> Von Benczur<sup>9</sup> and Geyelin<sup>14</sup> found that the influence of dilution on "d" readings was limited and without effect in the range of normal twenty-four hour urines, although allowance must be made when the quantities were abnormally large or small. In the experiments reported, such marked variations in urinary output occurred from day to day that the necessity of considering the effect of dilution was obvious.

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19. Wohlgemuth and Noguchi: Berl. klin. Wehnschr., 1912, xlix, 1096. This method is described in detail by Geyelin (Note 14) and therefore the description is not repeated here.

In the experiments with blood, 5 c.c. were withdrawn and defibrinated by shaking with beads. The serum was obtained by centrifugalization, and its "d" reading made by the method mentioned. Folin and Denis<sup>20</sup> micromethod on oxalated blood was used for the blood nitrogen determinations.

## EXPERIMENTS

*Experiment 1.*—Rabbit killed on the *first day* after the administration of the uranium nitrate.

First day. (Wt. 1,650 gm.)	
Urine: twenty-four-hour amount.....	150 c.c.
"d" .....	32
absolute diastatic strength.....	2,400
Blood: serum "d" .....	32
non-protein nitrogen (per 100 gm.).....	37 mg.
Administered 3 mg. uranium nitrate.	
Second day. (Wt. 1,700 gm.)	
Urine: twenty-four-hour amount .....	150 c.c.
"d" .....	32
absolute diastatic strength.....	2,400
Blood: serum "d" .....	32
non-protein nitrogen (per 100 gm.).....	54

Histological findings: Glomeruli negative; tubules negative. No pathological changes found in the kidney.

*Experiment 2.*—Rabbit killed on the *second day* after the administration of the uranium nitrate.

First day. (Wt. 1,600 gm.)	
Urine: twenty-four-hour amount .....	150 c.c.
"d" .....	32
absolute diastatic strength.....	2,400
Blood: serum "d" .....	64
non-protein nitrogen (per 100 gm.).....	25 mg.
Administered 6 mg. uranium nitrate.	
Second day. (Wt. 1,700 gm.)	
Urine: twenty-four-hour amount .....	180 c.c.
"d" .....	32
absolute diastatic strength.....	2,880
Third day. (Wt. 1,700 gm.)	
Urine: twenty-four-hour amount .....	150 c.c.
"d" .....	64
absolute diastatic strength.....	4,800
Blood: serum "d" .....	64
non-protein nitrogen (per 100 gm.).....	44 mg.

Histological Findings: Glomeruli negative; slight necrosis and desquamation of the epithelium of certain tubules; a few tubules filled with necrotic material; a few areas of round cell infiltration.

*Experiment 3.*—Rabbit killed on the *third day* after the administration of the uranium nitrate.

First day. (Wt. 2,600 gm.)	
Urine: twenty-four-hour amount .....	150 c.c.
"d" .....	128
absolute diastatic strength .....	9,600
Blood: serum "d" .....	64
non-protein nitrogen (per 100 gm.).....	37 mg.
Administered 6 mg. uranium nitrate.	

20. Folin and Denis: Jour. Biol. Chem., 1912, xi, 257.

Second day. (Wt. 2,600 gm.)

Urine: twenty-four-hour amount	160 c.c.
"d"	128
absolute diastatic strength	10,240

Third day. (Wt. 2,500 gm.)

Urine: twenty-four-hour amount	80 c.c.
"d"	128
absolute diastatic strength	5,120

Fourth day. (Wt. 2,450 gm.)

Urine: twenty-four-hour amount	7 c.c.
"d"	64
absolute diastatic strength	224
Blood: serum "d"	128
non-protein nitrogen (per 100 gm.)	131 mg.

Histological Findings: Glomeruli negative. Considerable necrosis and desquamation of tubular epithelium; many tubules filled with necrotic epithelium and casts; many tubules lined with regenerating epithelium.

*Experiment 4.*—Rabbit killed on the *fourth day* after the administration of uranium nitrate.

First day. (Wt. 2,150 gm.)

Urine: twenty-four-hour amount	110 c.c.
"d"	128
absolute diastatic strength	7,040
Blood: serum "d"	64
non-protein nitrogen (per 100 gm.)	30 mg.

Administered 7 mg. uranium nitrate.

Second day. (Wt. 2,050 gm.)

Urine: twenty-four-hour amount	100 c.c.
"d"	128
absolute diastatic strength	6,400

Third day. (Wt. 2,000 gm.)

Urine: twenty-four-hour amount	90 c.c.
"d"	128
absolute diastatic strength	5,760

Fourth day. (Wt. 1,930 gm.)

Urine: twenty-four-hour amount	8 c.c.
"d"	32
absolute diastatic strength	128

Fifth day. (Wt. 1,950 gm.)

Urine: twenty-four-hour amount	Anuric
"d"	...
absolute diastatic strength	...
Blood: serum "d"	64
non-protein nitrogen (per 100 gm.)	196 mg.

Histological Findings: Glomeruli negative; considerable necrosis and desquamation of the epithelium of many tubules; many tubules filled with necrotic material, a few with casts; a few tubules lined with regenerating epithelium.

*Experiment 5.*—Rabbit killed on the *fifth day* after the administration of the uranium nitrate.

First day. (Wt. 2,050 gm.)

Urine: twenty-four-hour amount	180 c.c.
"d"	32
absolute diastatic strength	2,880
Blood: serum "d"	32
non-protein nitrogen (per 100 gm.)	31 mg.

Administered 5 mg. uranium nitrate.

Second day. (Wt. 2,000 gm.)

Urine: twenty-four-hour amount	170 c.c.
"d"	32
absolute diastatic strength	2,720

Third day. (Wt. 1,900 gm.)		
Urine: twenty-four-hour amount	100 c.c.	
"d"	32	
absolute diastatic strength	1,600	
Fourth day. (Wt. 1,900 gm.)		
Urine: twenty-four-hour amount	75 c.c.	
"d"	32	
absolute diastatic strength	1,200	
Fifth day. (Wt. 1,850 gm.)		
Urine: twenty-four-hour amount	80 c.c.	
"d"	32	
absolute diastatic strength	1,280	
Sixth day. (Wt. 1,850 gm.)		
Urine: twenty-four-hour amount	110 c.c.	
"d"	16	
absolute diastatic strength	880	
Blood: serum "d"	64	
non-protein nitrogen (per 100 gm.)	78 mg.	

Histological Findings: Glomeruli negative; considerable necrosis and desquamation of the epithelium of many tubules; a few tubules filled with necrotic material; many tubules lined with regenerating epithelium.

*Experiment 6.*—Rabbit killed on the *sixth day* after the administration of the uranium nitrate.

First day. (Wt. 2,100 gm.)		
Urine: twenty-four-hour amount	80 c.c.	
"d"	16	
absolute diastatic strength	640	
Blood: serum "d"	64	
non-protein nitrogen (per 100 gm.)	35 mg.	
Administered 7 mg. uranium nitrate.		
Second day. (Wt. 2,100 gm.)		
Urine: twenty-four-hour amount	65 c.c.	
"d"	64	
absolute diastatic strength	2,080	
Third day. (Wt. 2,100 gm.)		
Urine: twenty-four-hour amount	100 c.c.	
"d"	64	
absolute diastatic strength	3,200	
Fourth day. (Wt. 2,000 gm.)		
Urine: twenty-four-hour amount	60 c.c.	
"d"	64	
absolute diastatic strength	1,920	
Fifth day. (Wt. 2,000 gm.)		
Urine: twenty-four-hour amount	10 c.c.	
"d"	4	
absolute diastatic strength	20	
Sixth day. (Wt. 2,000 gm.)		
Urine: twenty-four-hour amount	20 c.c.	
"d"	8	
absolute diastatic strength	80	
Seventh day. (Wt. 2,000 gm.)		
Urine: twenty-four-hour amount	30 c.c.	
"d"	4	
absolute diastatic strength	60	
Blood: serum "d"	128	
non-protein nitrogen (per 100 gm.)	217 mg.	

Histological findings: Ivaline droplets in many glomeruli; considerable necrosis and desquamation of the epithelium of many tubules; many tubules filled with necrotic material and casts; many tubules lined with regenerating epithelium.

*Experiment 7.*—Rabbit killed on the *seventh day* after the administration of the uranium nitrate.

First day. (Wt. 2,300 gm.)		
Urine: twenty-four-hour amount	130 c.c.	
"d"	16	
absolute diastatic strength	1,040	
Blood: serum "d"	32	
non-protein nitrogen (per 100 gm.)	38 mg.	
Administered 7 mg. uranium nitrate.		
Second day. (Wt. 2,250 gm.)		
Urine: twenty-four-hour amount	15 c.c.	
"d"	32	
absolute diastatic strength	240	
Third day. (Wt. 2,200 gm.)		
Urine: twenty-four-hour amount	200 c.c.	
"d"	32	
absolute diastatic strength	3,200	
Fourth day. (Wt. 2,150 gm.)		
Urine: twenty-four-hour amount	130 c.c.	
"d"	16	
absolute diastatic strength	1,040	
Fifth day. (Wt. 1,950 gm.)		
Urine: twenty-four-hour amount	70	
"d"	16	
absolute diastatic strength	560	
Sixth day. (Wt. 2,000 gm.)		
Urine: twenty-four-hour amount	100 c.c.	
"d"	16	
absolute diastatic strength	800	
Seventh day. (Wt. 1,900 gm.)		
Urine: twenty-four-hour amount	170 c.c.	
"d"	12	
absolute diastatic strength	1,020	
Eighth day. (Wt. 1,700 gm.)		
Urine: twenty-four-hour amount	120 c.c.	
"d"	16	
absolute diastatic strength	960	
Blood: Serum "d"	128	
non-protein nitrogen (per 100 gm.)	250 mg.	

Histological Findings: Glomeruli negative; desquamation of the epithelium of a few tubules; many tubules filled with serum and casts; many tubules lined with regenerating epithelium; slight increase in connective tissue throughout the kidney, suggesting preexisting chronic nephritis.

*Experiment 8.*—Rabbit killed on the *eighth day* after the administration of the uranium nitrate.

First day. (Wt. 1,500 gm.)		
Urine: twenty-four-hour amount	140 c.c.	
"d"	32	
absolute diastatic strength	2,240	
Blood: serum "d"	64	
non-protein nitrogen (per 100 gm.)	27 mg.	
Administered 4 mg. uranium nitrate.		
Second day. (Wt. 1,450 gm.)		
Urine: twenty-four-hour amount	150 c.c.	
"d"	32	
absolute diastatic strength	2,400	
Third day. (Wt. 1,500 gm.)		
Urine: twenty-four-hour amount	110 c.c.	
"d"	32	
absolute diastatic strength	1,760	

Fourth day. (Wt. 1,500 gm.)		
Urine: twenty-four-hour amount	170 c.c.	
"d"	16	
absolute diastatic strength	1,360	
Fifth day. (Wt. 1,450 gm.)		
Urine: twenty-four-hour amount	120 c.c.	
"d"	16	
absolute diastatic strength	960	
Sixth day. (Wt. 1,450 gm.)		
Urine: twenty-four-hour amount	120 c.c.	
"d"	16	
absolute diastatic strength	960	
Seventh day. (Wt. 1,400 gm.)		
Urine: twenty-four-hour amount	120 c.c.	
"d"	16	
absolute diastatic strength	960	
Eighth day. (Wt. 1,350 gm.)		
Urine: twenty-four-hour amount	130 c.c.	
"d"	16	
absolute diastatic strength	1,040	
Ninth day. (Wt. 1,300 gm.)		
Urine: twenty-four-hour amount	75 c.c.	
"d"	32	
absolute diastatic strength	1,200	
Blood: serum "d"	64	
non-protein nitrogen (per 100 gm.)	83 mg.	

Histological Findings: Glomeruli negative; desquamation of the epithelium of a few tubules; many tubules filled with casts and a few with necrotic cells; a few tubules lined with regenerating epithelium.

*Experiment 9.*—Rabbit killed on the *ninth day* after the administration of uranium nitrate.

First day. (Wt. 2,000 gm.)		
Urine: twenty-four-hour amount	180 c.c.	
"d"	32	
absolute diastatic strength	2,880	
Blood: serum "d"	32	
non-protein nitrogen (per 100 gm.)	39 mg.	
Administered 4 mg. uranium nitrate.		
Second day. (Wt. 2,100 gm.)		
Urine: twenty-four-hour amount	140 c.c.	
"d"	64	
absolute diastatic strength	4,680	
Third day. (Wt. 2,150 gm.)		
Urine: twenty-four-hour amount	150 c.c.	
"d"	32	
absolute diastatic strength	2,400	
Fourth day. (Wt. 2,100 gm.)		
Urine: twenty-four-hour amount	230 c.c.	
"d"	32	
absolute diastatic strength	3,680	
Fifth day. (Wt. 2,100 gm.)*		
Urine: twenty-four-hour amount	210 c.c.	
"d"	32	
absolute diastatic strength	3,360	
Sixth day. (Wt. 2,050 gm.)		
Urine: twenty-four-hour amount	180 c.c.	
"d"	64	
absolute diastatic strength	5,760	

\* On the fifth day the animal received an additional injection of 7 mg. of uranium nitrate.



Seventh day. (Wt. 2,050 gm.)	
Urine: twenty-four-hour amount.....	150 c.c.
"d" .....	64
absolute diastatic strength.....	4,800
Eighth day. (Wt. 1,950 gm.)	
Urine: twenty-four-hour amount.....	100 c.c.
"d" .....	32
absolute diastatic strength.....	1,600
Ninth day. (Wt. 1,950 gm.)	
Urine: twenty-four-hour amount.....	90 c.c.
"d" .....	32
absolute diastatic strength.....	1,440
Tenth day. (Wt. 1,900 gm.)	
Urine: twenty-four-hour amount.....	100 c.c.
"d" .....	32
absolute diastatic strength.....	1,600
Blood: serum "d" .....	64
non-protein nitrogen (per 100 gm.).....	96 mg.

Histological Findings: Glomeruli negative; a few tubules lined with regenerating epithelium; many tubules filled with casts.

*Experiment 10.*—Rabbit killed on the tenth day after the administration of uranium nitrate.

First day. (Wt. 2,300 gm.)	
Urine: twenty-four-hour amount.....	180 c.c.
"d" .....	64
absolute diastatic strength.....	5,760
Blood: serum "d" .....	64
non-protein nitrogen (per 100 gm.).....	30 mg.
Administered 6 mg. uranium nitrate.	
Second day. (Wt. 2,300 gm.)	
Urine: twenty-four-hour amount.....	120 c.c.
"d" .....	64
absolute diastatic strength.....	3,840
Third day. (Wt. 2,300 gm.)	
Urine: twenty-four-hour amount.....	180 c.c.
"d" .....	64
absolute diastatic strength.....	5,760
Fourth day. (Wt. 2,350 gm.)	
Urine: twenty-four-hour amount.....	90 c.c.
"d" .....	64
absolute diastatic strength.....	2,850
Fifth day. (Wt. 2,250 gm.)	
Urine: twenty-four-hour amount.....	170 c.c.
"d" .....	32
absolute diastatic strength.....	2,720
Sixth day. (Wt. 2,200 gm.)	
Urine: twenty-four-hour amount.....	210 c.c.
"d" .....	32
absolute diastatic strength.....	3,360
Seventh day. (Wt. 2,150 gm.)	
Urine: twenty-four-hour amount.....	170 c.c.
"d" .....	64
absolute diastatic strength.....	5,440
Eighth day. (Wt. 2,150 gm.)	
Urine: twenty-four-hour amount.....	220 c.c.
"d" .....	50
absolute diastatic strength.....	5,500
Ninth day. (Wt. 2,150 gm.)	
Urine: twenty-four-hour amount.....	190 c.c.
"d" .....	64
absolute diastatic strength.....	6,080

Tenth day. (Wt. 2,200 gm.)		
Urine: twenty-four-hour amount.....	170 c.c.	
"d" .....	64	
absolute diastatic strength.....	5,440	
Eleventh day. (Wt. 2,250 gm.)		
Urine: twenty-four-hour amount.....	170 c.c.	
"d" .....	64	
absolute diastatic strength.....	5,440	
Blood: serum "d".....	64	
non-protein nitrogen (per 100 gm.).....	24 mg.	
Histological Findings: Glomeruli negative; a few tubules filled with casts.		

From Experiments 1 to 10 recorded above, it is seen that the findings in regard to the non-protein nitrogen of the blood confirm those recorded by Frothingham, Fitz, Folin and Denis.<sup>15</sup> The accumulation of nitrogen was gradual. It became high after the third day, remained at a high level from the third to the eighth day, and then gradually returned to normal. When extensive necrosis of the renal epithelium occurred, the blood nitrogen accumulated rapidly, and diminished slowly with repair of the kidney. Thus this test paralleled in a general way the anatomical damage in the kidney.

The amylase readings in the urine varied considerably in animals supposed to be normal. The "d" readings ran from 16 to 128 units, and the "absolute diastatic strength" from 640 to 5,760 units. This may in part be due to the fact that the animals were not kept under a longer period of preliminary observation. They were taken from stock and injected with uranium nitrate after one twenty-four hour specimen of urine was collected. Nevertheless the blood nitrogen and the blood "d" readings were much more constant under the same conditions.

In six of the ten experiments there was an increase in the "absolute diastatic strength" of the urine, and in two experiments of the "d" reading, following the injection of the uranium nitrate. This lasted for a short time. It was not caused by an increased output of urine in every case, and suggested a stimulated renal function which was not confirmed, however, by a diminished blood nitrogen.

The "absolute diastatic strength" and the "d" of the urine diminished in each case as the nephritis became severe. Both readings paralleled roughly the severity of the lesion as judged by anatomical changes in the kidney. The "absolute diastatic strength" seemed to show finer distinctions in regard to the renal function than did the "d" readings. This was largely because of the variations in the twenty-four hour urine which occurred from day to day.

The blood "d" readings did not increase as much as would be presumed from the variations in the excretion of amylase. In four cases there was a definite rise in "d" at the end of the experiment when the nephritis was most severe. It did not parallel the accumulation of blood nitrogen, nor accompany an extremely low amylase excretion in

each case and was not sufficiently marked to make the determinations of particular diagnostic or prognostic value.

Thus on the whole, in the individual cases there was a definite relation between the nephritis, the accumulation of non-protein nitrogen in the blood, and the excretion of amylase in the urine. The blood "d" readings were insignificant.

In order to compare more accurately the relation of the accumulation of the non-protein nitrogen in the blood with the excretion of amylase at different stages of the acute nephritis, a second series of experiments was made. In this series the blood was collected every day from the ear veins and the amylase excretion was followed. Experiments 11 to 19 recorded below, give the important points of these observations.

*Experiment 11.*—Rabbit killed on the *fourth day* after the administration of uranium nitrate.

First day. (Wt. 1,700 gm.)	
Urine: twenty-four-hour amount.....	143 c.c.
"d" .....	128
absolute diastatic strength.....	9,152
Blood: non-protein nitrogen (per 100 gm.).....	24 mg.
Administered 3 mg. uranium nitrate.	
Third day. (Wt. 1,800 gm.)	
Urine: twenty-four-hour amount.....	120 c.c.
"d" .....	64
absolute diastatic strength.....	3,840
Blood: non-protein nitrogen (per 100 gm.).....	30 mg.
Fifth day. (Wt. 1,550 gm.)	
Urine: twenty-four-hour amount.....	15 c.c.
absolute diastatic strength.....	120
Blood: non-protein nitrogen (per 100 gm.).....	125 mg.

Histological Findings: Glomeruli negative; considerable necrosis and desquamation of the epithelium of certain tubules; many other tubules filled with necrotic material and casts; a few other tubules lined with regenerated epithelium; a few areas of round-cell infiltration.

*Experiment 12.*—Rabbit found dead on *sixth day* after the administration of uranium nitrate.

First day. (Wt. 2,500 gm.)	
Urine: twenty-four-hour amount.....	105 c.c.
"d" .....	256
absolute diastatic strength.....	13,440
Blood: non-protein nitrogen (per 100 gm.).....	28 mg.
Administered 4 mg. uranium nitrate.	
Fourth day. (Wt. 2,550 gm.)	
Urine: twenty-four-hour amount .....	135 c.c.
"d" .....	64
absolute diastatic strength.....	4,320
Blood: non-protein nitrogen (per 100 gm.) .....	51 mg.
Fifth day. (Wt. 2,500 gm.)	
Urine: twenty-four-hour amount.....	60 c.c.
"d" .....	128
absolute diastatic strength.....	3,840
Blood: non-protein nitrogen (per 100 gm.).....	80 mg.

Sixth day. (Wt. 2,500 gm.)

Urine: twenty-four-hour amount .....	10 c.c.
"d" .....	128
absolute diastatic strength.....	640
Blood: non-protein nitrogen (per 100 gm.).....	125 mg.

Histological Findings: Glomeruli congested; considerable necrosis and desquamation of the epithelium of certain tubules; many other tubules filled with necrotic material and casts; a few other tubules lined with regenerated epithelium.

*Experiment 13.*—Rabbit found dead on sixth day after the administration of uranium nitrate.

First day. (Wt. 2,300 gm.)

Urine: twenty-four-hour amount.....	100 c.c.
"d" .....	64
absolute diastatic strength.....	3,200
Blood: non-protein nitrogen (per 100 gm.).....	25 mg.
Administered 8 mg. uranium nitrate.	

Third day. (Wt. 2,350 gm.)

Urine: twenty-four-hour amount.....	40 c.c.
"d" .....	128
absolute diastatic strength.....	2,560
Blood: non-protein nitrogen (per 100 gm.).....	41 mg.

Fourth day. (Wt. 2,350 gm.)

Urine: twenty-four-hour amount .....	3 c.c.
"d" .....	32
absolute diastatic strength.....	48
Blood: non-protein nitrogen (per 100 gm.).....	70 mg.

Fifth day. (Wt. 2,300 gm.)

Urine: twenty-four-hour amount.....	5 c.c.
"d" .....	2
absolute diastatic strength.....	5
Blood: non-protein nitrogen (per 100 gm.).....	96 mg.

Sixth day. (Wt. 2,300 gm.)

Urine: twenty-four-hour amount.....	7 c.c.
"d" .....	16
absolute diastatic strength.....	56
Blood: non-protein nitrogen (per 100 gm.).....	125 mg.

Histological Findings: Glomeruli negative; necrosis and desquamation of the epithelium of certain tubules; few tubules filled with necrotic material, but many filled with casts; many tubules lined with regenerated epithelium.

*Experiment 14.*—Rabbit killed on the seventh day after the administration of uranium nitrate.

First day. (Wt. 2,000 gm.)

Urine: twenty-four-hour amount.....	120 c.c.
"d" .....	128
absolute diastatic strength.....	7,680
Blood: non-protein nitrogen (per 100 gm.).....	30 mg.
Administered 2.5 mg. uranium nitrate.	

Second day. (Wt. 1,950 gm.)

Urine: twenty-four-hour amount.....	170 c.c.
"d" .....	128
absolute diastatic strength.....	10,880
Blood: non-protein nitrogen (per 100 gm.).....	35 mg.

Fourth day. (Wt. 1,950 gm.)

Urine: twenty-four-hour amount.....	17 c.c.
"d" .....	256
absolute diastatic strength.....	2,176
Blood: non-protein nitrogen (per 100 gm.).....	136 mg.

Sixth day. (Wt. 1,950 gm.)		
Urine: twenty-four-hour amount.....	20 c.c.	
"d" .....	4	
absolute diastatic strength.....	40	
Blood: non-protein nitrogen (per 100 gm.).....	200 mg.	
Seventh day. (Wt. 1,950 gm.)		
Urine: twenty-four-hour amount.....	8 c.c.	
"d" .....	8	
absolute diastatic strength.....	32	
Blood: non-protein nitrogen (per 100 gm.).....	238 mg.	

Histological Findings: Glomeruli negative; considerable necrosis and desquamation of the epithelium of certain tubules; many tubules filled with necrotic material and casts; many tubules lined with regenerated epithelium.

*Experiment 15.*—Experiment discontinued on the ninth day after the administration of the uranium nitrate.

First day. (Wt. 2,700 gm.)		
Urine: twenty-four-hour amount.....	150 c.c.	
"d" .....	128	
absolute diastatic strength.....	9,600	
Blood: non-protein nitrogen (per 100 gm.).....	27 mg.	
Administered 4 mg. uranium nitrate.		
Third day. (Wt. 2,650 gm.)		
Urine: twenty-four-hour amount.....	200 c.c.	
"d" .....	64	
absolute diastatic strength.....	6,400	
Blood: non-protein nitrogen (per 100 gm.).....	37 mg.	
Fifth day. (Wt. 2,600 gm.)		
Urine: twenty-four-hour amount.....	180 c.c.	
"d" .....	64	
absolute diastatic strength.....	5,760	
Blood: non-protein nitrogen (per 100 gm.).....	71 mg.	
Seventh day. (Wt. 2,450 gm.)		
Urine: twenty-four-hour amount.....	100 c.c.	
"d" .....	200	
absolute diastatic strength.....	10,000	
Blood: non-protein nitrogen (per 100 gm.).....	54 mg.	
Ninth day. (Wt. 2,350 gm.)		
Urine: twenty-four-hour amount.....	100 c.c.	
"d" .....	128	
absolute diastatic strength.....	6,400	
Blood: non-protein nitrogen (per 100 gm.).....	43 mg.	

*Experiment 16.*—Rabbit killed on the tenth day after the administration of uranium nitrate.

First day. (Wt. 2,700 gm.)		
Urine: twenty-four-hour amount.....	220 c.c.	
"d" .....	64	
absolute diastatic strength.....	7,040	
Blood: non-protein nitrogen (per 100 gm.).....	38 mg.	
Administered 4 mg. uranium nitrate.		
Third day. (Wt. 2,700 gm.)		
Urine: twenty-four-hour amount.....	220 c.c.	
"d" .....	128	
absolute diastatic strength.....	14,080	
Blood: non-protein nitrogen (per 100 gm.).....	46 mg.	
Fifth day. (Wt. 2,600 gm.)		
Urine: twenty-four-hour amount.....	50 c.c.	
"d" .....	64	
absolute diastatic strength.....	1,600	
Blood: non-protein nitrogen (per 100 gm.).....	102 mg.	

Sixth day. (Wt. 2,500 gm.)	
Urine: twenty-four-hour amount.....	70 c.c.
"d".....	24
absolute diastatic strength.....	840
Blood: non-protein nitrogen (per 100 gm.).....	161 mg.

Eighth day. (Wt. 2,300 gm.)	
Urine: twenty-four-hour amount.....	80 c.c.
"d".....	32
absolute diastatic strength.....	1,280
Blood: non-protein nitrogen (per 100 gm.).....	208 mg.

Tenth day. (Wt. 2,100 gm.)	
Urine: twenty-four-hour amount.....	140 c.c.
"d".....	64
absolute diastatic strength.....	4,680
Blood: non-protein nitrogen (per 100 gm.).....	165 mg.

Histological Findings: Glomeruli negative; epithelium of tubules negative; many tubules contain hyaline casts.

*Experiment 17.*—Rabbit found dead on the tenth day after the administration of the uranium nitrate.

First day. (Wt. 1,900 gm.)	
Urine: twenty-four-hour amount.....	100 c.c.
"d".....	128
absolute diastatic strength.....	6,400
Blood: non-protein nitrogen (per 100 gm.).....	34 mg.
Administered 2 mg. uranium nitrate.	

Third day. (Wt. 2,050 gm.)	
Urine: twenty-four-hour amount.....	95 c.c.
"d".....	64
absolute diastatic strength.....	3,040
Blood: non-protein nitrogen (per 100 gm.).....	41 mg.

Fifth day. (Wt. 2,050 gm.)	
Urine: twenty-four-hour amount.....	45 c.c.
"d".....	32
absolute diastatic strength.....	720
Blood: non-protein nitrogen (per 100 gm.).....	113 mg.

Seventh day. (Wt. 1,900 gm.)	
Urine: twenty-four-hour amount.....	90 c.c.
"d".....	32
absolute diastatic strength.....	1,440
Blood: non-protein nitrogen (per 100 gm.).....	208 mg.

Eighth day. (Wt. 1,800 gm.)	
Urine: twenty-four-hour amount.....	185 c.c.
"d".....	32
absolute diastatic strength.....	2,960
Blood: non-protein nitrogen (per 100 gm.).....	250 mg.

Tenth day. (Wt. 1,550 gm.)	
Urine: twenty-four-hour amount.....	200 c.c.
"d".....	32
absolute diastatic strength.....	3,200
Blood: non-protein nitrogen (100 per gm.).....	151 mg.

Histological Findings: Glomeruli negative. A few tubules filled with necrotic material; many tubules filled with hyaline casts; a few tubules lined with regenerating epithelium. A few areas of round-cell infiltration.

*Experiment 18.*—Experiment discontinued on the thirteenth day after the administration of uranium nitrate.

First day. (Wt. 2,200 gm.)	
Urine: twenty-four-hour amount.....	160 c.c.
"d".....	128
absolute diastatic strength.....	10,240
Blood: non-protein nitrogen (per 100 gm.).....	30 mg.
Administered 2.5 mg. uranium nitrate.	



Second day. (Wt. 2,200 gm.)		
Urine: twenty-four-hour amount.....	150	c.c.
"d" .....	128	
absolute diastatic strength.....	9,600	
Blood: non-protein nitrogen (per 100 gm.).....	39	mg.
Fourth day. (Wt. 2,100 gm.)		
Urine: twenty-four-hour amount.....	125	c.c.
"d" .....	32	
absolute diastatic strength.....	2,000	
Blood: non-protein nitrogen (per 100 gm.).....	83	mg.
Sixth day. (Wt. 2,000 gm.)		
Urine: twenty-four-hour amount.....	155	c.c.
"d" .....	32	
absolute diastatic strength.....	2,480	
Blood: non-protein nitrogen (per 100 gm.).....	104	mg.
Eighth day. (Wt. 1,900 gm.)		
Urine: twenty-four-hour amount.....	170	c.c.
"d" .....	64	
absolute diastatic strength.....	5,440	
Blood: non-protein nitrogen (per 100 gm.).....	96	mg.
Tenth day. (Wt. 1,950 gm.)		
Urine: twenty-four-hour amount.....	170	c.c.
"d" .....	64	
absolute diastatic strength.....	5,440	
Blood: non-protein nitrogen (per 100 gm.).....	83	mg.
Eleventh day. (Wt. 1,850 gm.)		
Urine: twenty-four-hour amount.....	210	c.c.
"d" .....	64	
absolute diastatic strength.....	6,720	
Blood: non-protein nitrogen (per 100 gm.).....	52	mg.
Thirteenth day. (Wt. 2,000 gm.)		
Urine: twenty-four-hour amount.....	110	c.c.
"d" .....	128	
absolute diastatic strength.....	7,040	
Blood: non-protein nitrogen (per 100 gm.).....	27	mg.

*Experiment 19.*—Experiment discontinued on the fifteenth day after the injection of uranium nitrate.

First day. (Wt. 2,500 gm.)		
Urine: twenty-four-hour amount.....	200	c.c.
"d" .....	100	
absolute diastatic strength.....	10,000	
Blood: non-protein nitrogen (per 100 gm.).....	29	mg.
Administered 6 mg. uranium nitrate.		
Second day. (Wt. 2,400 gm.)		
Urine: twenty-four-hour amount.....	170	c.c.
"d" .....	100	
absolute diastatic strength.....	8,500	
Blood: non-protein nitrogen (per 100 gm.).....	43	mg.
Fifth day. (Wt. 2,350 gm.)		
Urine: twenty-four-hour amount.....	200	c.c.
"d" .....	12	
absolute diastatic strength.....	1,200	
Blood: non-protein nitrogen (per 100 gm.).....	54	mg.
Seventh day. (Wt. 2,400 gm.)		
Urine: twenty-four-hour amount.....	150	c.c.
"d" .....	16	
absolute diastatic strength.....	1,200	
Blood: non-protein nitrogen (per 100 gm.).....	74	mg.
Tenth day. (Wt. 2,100 gm.)		
Blood: non-protein nitrogen (per 100 gm.).....	78	mg.

Thirteenth day. (Wt. 2,200 gm.)		
Urine: twenty-four-hour amount.....	150 c.c.	
"d" .....	32	
absolute diastatic strength.....	2,400	
Blood: non-protein nitrogen (per 100 gm.).....	40 mg.	
Fifteenth day. (Wt. 2,400 gm.)		
Urine: twenty-four-hour amount.....	170 c.c.	
"d" .....	64	
absolute diastatic strength.....	5,440	
Blood: non-protein nitrogen (per 100 gm.).....	31 mg.	

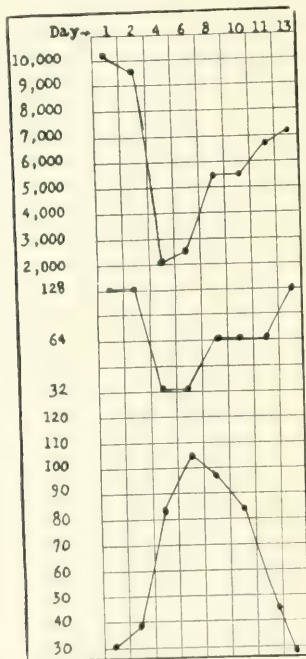


Chart 1.—Curves showing "absolute diastatic" strength (upper curve), "d" excretion (middle curve), and (lower curve) non-protein nitrogen retention in a moderate nephritis (Exp. 18).

The correspondence between the results of the amylase tests and those of the blood analyses in Experiments 11 to 19 is shown graphically in the accompanying charts, (a) with reference to a moderate degree of nephritis (Exp. 18), (b) with reference to severe nephritis (Exp. 17).

From the tables and charts it is clear that at the beginning of the nephritis the "absolute diastatic strength" of the urine dropped more rapidly than the accumulation of the non-protein nitrogen of the blood. During the course of the disease the height of the nitrogenous accumu-

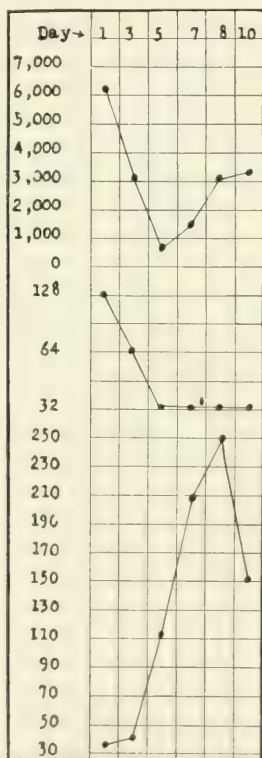


Chart 2.—Curves showing "absolute diastatic" strength (upper curve), "d" excretion (middle curve), and (lower curve) non-protein nitrogen retention in a severe nephritis (Exp. 17).

lation was reached later than the lowest level of the amylase excretion. After the kidney function had begun to improve as shown by an increasing elimination of amylase, the retention nitrogen did not at once begin to recede but even continued to rise for a short period.

Thus the amylase test is very similar to the phenolsulphonephthalein test. It has certain disadvantages. In a series of nineteen rabbits, the normal excretion showed such marked variation that the information obtained from the test could only be applied to the individual case. Therefore in studying the renal function of any one it was first necessary to discover the normal excretion for that animal. It is only fair to state, however, that the results obtained in man by other observers tend to show that there is much less normal individual variation than in the experiments reported here. A second disadvantage with the test is that it is less quantitative than the phenolsulphonephthalein test. If the "absolute diastatic strength" is taken, small changes in the output of urine may exaggerate changes in renal function. If the "d" reading is accepted, slight changes in renal function are overlooked. Possibly a different method of diluting the urine, as suggested by Brown and Smith,<sup>21</sup> may obviate this source of error.

On the whole, these experiments show that there is a close parallelism between the modes of excretion of phenolsulphonephthalein and amylase, and that amylase like phenolsulphonephthalein diminishes with an increasing nephritis, returns to normal with improvement of renal function, and is not influenced by blood retention to the same extent as is the accumulation of non-protein nitrogen.

#### CONCLUSIONS

1. In acute uranum nephritis in rabbits, the excretion of amylase in the urine and the amount of non-protein nitrogen in the blood vary from the normal during the course of the nephritis and return to normal as the nephritis heals.

2. In individual cases the degree of variation from the normal agrees on the whole with the amount of destruction demonstrated histologically in the kidney.

3. The amylase excretion, like that of phenolsulphonephthalein, drops rapidly to its lowest point and returns rapidly toward its previous level with recovery of the kidney. It is but little influenced by accumulation in the blood.

4. The non-protein nitrogen accumulates gradually in the blood, and returns to normal gradually as the kidney recovers.

5. Amylase excretion as a test for renal function is similar to phenolsulphonephthalein, but is less delicate.

6. The amylase and phenolsulphonephthalein tests show the renal function at the moment; the blood nitrogen test is more influenced by the duration of the condition causing its accumulation.

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21. Brown and Smith: Bull. Johns Hopkins Hosp., 1914, xxv, 213.

## FURTHER STUDIES OF RENAL FUNCTION IN RENAL, CARDIORENAL AND CARDIAC DISEASES \*

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The objects of this investigation are (1) to ascertain the value of quantitative determinations of the diastatic activity<sup>1</sup> of urine in revealing renal functional capacity in cardiac, cardiorenal and renal cases; (2) to compare in the same group of cases the findings of diastase, urea and phthalein in the urine with those of urea, total incoagulable nitrogen and cryoscopy in the blood, and (3) to compare the relative value and limitations of the tests of retention with those of excretion.

Renal functional capacity is usually ascertained in one of two ways: (1) *Tests of excretory capacity* through the quantitative determination of the secretion of various substances in the urine — dyes, methylene blue, indigocarmin, rosanilin and phthalein; other chemicals, potassium iodid, lactose, salicylates, sodium chlorid, urea, sugar following phloridzin and the enzyme, diastase. (2) *Tests of retention* through the determination of the concentration of certain substances in the blood, ions — through electrical conductivity, molecules and ions — through cryoscopy, and urea, total incoagulable nitrogen and cholesterolin.

The number of functional tests has increased to such an extent that it is essential to determine which can be discarded without loss. Only through familiarity with the reliability, value, limitations, peculiarities, and the significance of the findings of each test in the various types of disease is the most profitable selection of tests made possible.

### THE TESTS EMPLOYED AND THEIR TECHNIC

1. The *phthalein* test<sup>2</sup> was used according to the usual technic.
2. *Diastase*.<sup>3</sup> Diastase has recently been introduced into functional renal work by Wohlgemuth<sup>4</sup> for determining the relative functional

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1. The expression "diastatic activity of the urine" is used in place of "diastase content" or "quantitative urinary diastase," because at present we have no method for the quantitative estimation of an enzyme, but only methods for the quantitative expression of relative enzymatic activity.

2. Rowntree and Geraghty: *THE ARCHIVES INT. MED.*, 1912, ix, 284.

3. For the results of our diastase studies in unilateral and bilateral surgical diseases of the kidneys, see *Ann. Surg.*, 1913, xxxvii, 801; *Surg., Gynec. and Obst.*, 1914, xviii, 196.

4. Wohlgemuth: *Biol. Ztschr.*, 1909, xxi, 432.

capacity of the two kidneys. A modification of this method was devised by us to make the test adaptable for determining total renal functional capacity. The technic employed was elaborated in conjunction with Dr. Thomas R. Brown, who has demonstrated with it that the total daily output in urine is fairly constant.<sup>5</sup> The technic was as follows:

One-fifth of the twenty-four-hour urine collected under toluol was neutralized and diluted to 1 L. By means of a graduated 2 c.c. pipet, decreasing amounts of urine were placed in a series of twelve tubes (arranged in a rack) as follows: 1.8, 1.6, 1.4, 1.2, 1, 0.8, 0.6, 0.4 c.c. Ten c.c. of the diluted urine was further diluted to 20 c.c. and of this decreasing amounts placed in the remaining tubes of the series as follows: 0.4, 0.2, 0.1, 0.05 c.c. To each tube was added sufficient 1 per cent. NaCl solution to bring the total volume in each tube to 2 c.c. Two c.c. of a 0.1 per cent. freshly prepared soluble starch solution was added to each tube. The rack with the tubes was placed in a water-bath at 38 C. for a half-hour, then transferred to cold water for three minutes.

$\frac{N}{50}$  iodine solution was added drop by drop in amounts sufficient to elicit a permanent color. The occurrence of blue or violet shows incomplete digestion, while the last tube without the violet color indicates the diastatic activity of the urine and from it "d" is calculated. The diastatic activity is expressed by  $d \frac{38^\circ}{30'}$ , which represents the number of c.c. of 0.1 per cent. starch solution which 1 c.c. of the diluted urine can digest at 38 C. in thirty minutes to products not yielding a blue color with iodine.

The urea content of the twenty-four-hour specimens of urine was determined by the Marshall method.<sup>6</sup>

The principle of Marshall's method consists in the conversion of the urea into ammonium carbonate by means of an enzyme, urease, present in an extract of the soy bean, and the titration of the ammonia with standard hydrochloric acid and methyl orange, directly or after its removal with an air current.

The freezing point of serum was made in the ordinary way, utilizing the Beckman apparatus, 25 to 50 c.c. of blood usually being taken.

The blood urea was determined according to Marshall's<sup>7</sup> method.

The total non-protein nitrogen of the serum was determined as follows: Ten c.c. of serum was added to 115 c.c. of 95 per cent. alcohol, 100 c.c. of the filtrate being evaporated to dryness. The residue was subjected to Kjeldahl nitrogen determination. The result represents the nitrogen in 8 c.c. of blood.

The values which we accept as normal are as follows: Phthalein, 50 to 60 per cent. for one hour, 60 to 80 per cent. for two hours,  $d \frac{38^\circ}{30'} = 5$  or more, freezing point of serum  $-56^\circ$ , total non-protein N of blood .22 — .26 gm. per L. as determined by Folin, and blood urea .20 — .30 gm. per L. Retention of a mild grade occurs in many conditions without apparently serious renal involvement. Only when the retention is considerable do we consider the findings of importance. Such retention we refer to as cumulative phenomena, which means that the freezing-point of blood is at least  $-0.60$  C., the total non-protein nitrogen 0.500 gm. and the urea of blood 0.550 gm. per L.

5. Brown and Smith: Bull. Johns Hopkins Hosp., July, 1914.

6. Marshall: Jour. Biol. Chem., 1913, xiv, 283; xv, 495.

7. Marshall: Jour. Biol. Chem., 1913, xv, 487.



TABLE 1.—GROUP A. MILD NEPHRITIS

No.	Name	Date	Clinical Diagnosis	Phthalain Per Cent.		Dis- tase 38° d — 30°	Albu- min	Urea in 24-hr. Urine Gm.	Crys- copy ( ) <sup>3</sup>	Urea per L. Blood Gm.	Total Non- protein N per L. Blood Gm.	Remarks
				1 hr.	2 hr.							
1	B. 3174	3/29/13	Chronic nephritis; psychasthenia	37	21	0	+	13.5	0.56	0.380	....	Slight elevation of blood-pressure. Trace albumin and few casts in urine. Lactose positive in 6 hours. Discharged March 12, 1913.
2	E. Har- riet Lane	3/12/13	Orthostatic albumin- uria	5	55	2.5	—	8.3	....	....	....	Patented child of 12 years. Albumin dis- appeared in recumbent posture.
3	T. 30165	1/18/13	Familial albuminuria; mild typhoid fever	42	20	1.7	+	....	....	....	0.530	Trace of albumin present after recovery.
4	S. 30162	1/8/13	Acute nephritis.....	30	23	5	+	....	0.53	..	0.100	Nephritis following turpentine ingestion. Recovery without albuminuria. Guaiac positive.
5	P. 30492	3/12/13	Chronic nephritis; arterio-sclerosis	25	15	1.4	++	....	....	....	0.120	Lactose, 6 hours. Discharged, improved, March 14, 1913.
6	P. 30520	3/18/13	Chronic nephritis; neurasthenia	26	18	5	+	....	....	....	....	Discharged March 12, 1913.
7	H. 30506	3/7/13	Chronic nephritis; acute exacerbation	20	21	?	++	15.4	0.64	....	....	March 7, 1913, guaiac positive.
		3/31/13	.....	....	....	0	±	....	....	....	....	March 21, 1913, guaiac positive. Dis- charged April 19, 1913, improved.
8	C. 30653	11/8/13	Chronic nephritis; albuminuria	60	15	10	±	....	....	....	0.384	Discharged Nov. 14, 1913, unimproved.
9	C. ....	1/20/13	Chronic nephritis	49	16	20	±	....	....	....	0.185	Lactose normal.
10	L. ....	2/9/14	Albuminuria; mild nephritis	51	9	3.3	....	....	....	0.120	0.294	Lactose 12 hours. Guaiac positive. Dis- charged Feb. 18, 1914.
11	S. 32071	2/3/14	Acute nephritis.....	23	31	5	+	....	....	0.390	0.472	Lactose 6 hours. Guaiac positive. Dis- charged March 14, 1914, improved.
12	C. 32178	3/8/14	Mild nephritis.....	47	15	6.6	+	....	....	0.210	0.455	

## RESULTS

In a series of 56 cases of medical nephropathies, 60 diastase, 41 phthalein, 30 urea determinations in the urine, together with 27 freezing points, 44 urea or total incoagulable nitrogen estimations in the blood-serum have been made. Opportunity to compare the functional findings with the anatomical changes present in the kidney at autopsy has been afforded in fifteen instances. For ease of presentation and discussion of the results, the cases presented in the accompanying table have been grouped as previously<sup>8</sup> into Section A, mild nephritis; B, severe nephritis; C, myocardial insufficiency; D, cardiorenal disease.

*Group A—Mild Nephritis.*—Twelve cases fall into this group. The lowest phthalein encountered was 40 per cent. for two hours, yet no diastatic activity could be detected in two cases, while  $d \frac{38^\circ}{30'}$  was less than 2 in two other instances. Details concerning two of these cases can be seen from the following case reports:

CASE 1.—W. B., 31,744. The patient, a physician, aged 45, consulted Dr Barker concerning his shortness of breath. His family history was not of particular interest, nor was his past history, except for two attacks of gout and occipital headache persisting for years. Under strain the patient became weak, nervous and irritable.

For some years he had been aware of the fact that he had a slight albuminuria, a few casts and a slightly increased B. P. The blood picture was practically normal. The eye grounds normal except for slight blurring of upper and nasal margin. Except a B. P. varying from 130 to 160 the physical examination revealed nothing of importance. The Wassermann was negative.

CASE 5.—J. B. P., 30,492.—This patient, 64 years of age, had had the ordinary diseases of childhood, pneumonia as a young man, one attack of gonorrhea followed by stricture, pyorrhea alveolaris for twenty years and an attack of rheumatism fourteen years ago. For four years he has had to urinate once during the night.

Present illness dated back six weeks, starting with slight pain in region of left kidney. Urinalysis showed albumin and casts, whereupon his family sent him in for study.

Physical examination revealed slightly palpable radials, B. P. 135, an occasional extrasystole which later disappeared, and a faint aortic systolic murmur which frequently disappeared in erect posture. The Roentgen-ray showed slight dilatation of the arch. The blood picture was normal and the eye grounds showed slight blurring of part of margin of disc. The vessels were slightly tortuous, two small patches suggesting exudate in the left eye. There were no scars or hemorrhages in either eye.

In the remaining eight cases the diastatic findings were in harmony with those of the other tests, two cases showing but a slight reduction in diastatic activity, the others appearing normal.

The findings in Case 7 are interesting. This was considered an acute exacerbation, mild in type, in the course of a chronic nephritis. However, the phthalein was considerably reduced, 41 per cent. for

8. Rowntree and Fitz: THE ARCHIVES INT. MED., 1913, xi, 258.

TABLE 2.—GROUP B, SEVERE NEPHRITIS

No.	Name	Date	Clinical Diagnosis	Phthalein Per Cent.		Dis- taste d — 30°	Albu- min	Urea 24-hr. Urine Gm.	Crys- tals copy —( )	Urea per l. Blood Gm.	Total Non- protein Blood Gm.	Remarks
				1 hr.	2 hr.							
13	M. 30537	4/10/13	Chronic diffuse neph- ritis	±	±	1.4	+	....	0.83	....	....	Discharged April 29, 1913, improved.
14	K. M. ...	3/1/13 3/12/13	Chronic diffuse neph- ritis; arteriosclerosis	....	....	2.5 0	....	20.3	0.50	0.846	....	Diastase at March 12, 1913, 0. Patient better; discharged March 18, 1913.
15	R. 30258	1/18/13	Chronic diffuse neph- ritis	±	±	1.7	+++	....	....	....	1.000	Discharged Feb. 30, 1913, improved.
16	R. 30406	3/25/13	Chronic diffuse neph- ritis; arteriosclerosis	10	14	1.3	±	10.0	0.53	0.460	....	Discharged March 31, 1914, improved.
17	L. 30585	3/25/13	Paraneurymatous nephritis	....	....	0	++	10.5	....	....	....	Guinea ++. Discharged March 24, 1913, unimproved.
18	N. ....	12/9/12	Chronic nephritis; hemiplegia	....	....	1.3	0	....	0.61	....	....	Died one month later.
19	V. 30253	3/18/13	Paraneurymatous nephritis	58	12	5	++	11.5	0.50	....	0.160	Persistent edema over six months, heavy albumuria; reaction of NaCl.
20	... 30073	12/12/12	Chronic diffuse neph- ritis; uræmia	±	±	1.7	++	....	....	....	0.850 2.000	Discharged March 24, 1913, improved. Necropsy 3847.
21	S. 29680	12/8/12	Chronic diffuse neph- ritis; gout	±	±	1.7	+	....	....	....	0.500	Discharged Dec. 14, 1912, improved.
22	McC. 30286	1/21/13	Chronic diffuse neph- ritis; arteriosclerosis	30	14	1.7	±	....	....	....	0.080	Discharged Jan. 22, 1913.
23	W. 31769	10/8/13	Chronic nephritis...	10	7	5	....	....	....	....	1.030	Discharged Dec. 12, 1913, improved.
24	R. 31674	11/26/13	Chronic nephritis...	8	10	10	++	....	....	0.414	0.588	
25	F. 31862	12/10/13	Chronic nephritis...	22	18	2	+	....	....	....	0.322	Discharged Jan. 7, 1914, improved.
26	W. ....	1/28/14	Chronic nephritis...	30	6	0	+	....	....	0.340	0.420	Lactose 12 hours.

two hours (20 per cent. for first hour), which is the lowest phthalein in this group.  $D \frac{38^\circ}{30'}$  was only 2, while the freezing point was reduced to  $-.64$ . All the findings are in harmony and point to a more serious involvement than clinically was thought to exist. The drop in  $d \frac{38^\circ}{30'}$  to 0 three weeks later, at which time the albumin had practically disappeared, is inexplicable as the patient seemed much improved in every way and was discharged in good condition.

No evidence of cumulative phenomena has been encountered in this group except in the instance just referred to, in which the finding was in keeping with the phthalein and diastase findings.

It appears, therefore, that findings of all the tests are in harmony in nine of the twelve cases and that the findings of all the tests, with the exception of diastase, are in accord throughout. The diastatic activity has indicated severe functional involvement in three cases of nephritis in which the clinical picture, history, phthalein test, tests of retention and the subsequent course of events, all showed that the involvement was but slight.

*Group B—Severe Nephritis.*—Fourteen cases of severe nephritis were studied. The diastatic activity was decreased in all but three instances —  $d \frac{38^\circ}{30'}$  being 1.7 or lower in ten cases. Two of these patients died, but only one came to necropsy. Zero value for diastase was encountered three times. K. M., No. 14, showed a zero value shortly before leaving the hospital, at which time clinically he seemed much improved. Normal diastatic values were found in Nos. 19, 23 and 24.

In No. 19 the finding is in harmony with all other tests with the exception of salt, toward which a retention existed. The case is of great interest as an instance of hyperpermeability in nephritis and has been reported in detail. Normal diastase findings in Nos. 23 and 24 are irreconcilable with other findings, since the phthalein was markedly decreased and cumulative phenomena were present in both cases.

Depression of the freezing point to  $-.61$  was only once encountered (No. 18), the patient dying one month later. In the presence of very severe nephritis, the freezing point was not markedly decreased in three instances (Nos. 13, 14 and 16). Cumulative phenomena as evidenced by urea and total non-protein N of the blood were present in six cases. The low N content in Case 19<sup>9</sup> (referred to above) is of interest in connection with the high freezing point and normal phthalein

<sup>9</sup> This case has been classed as severe nephritis because of clinical findings—marked albuminuria and considerable edema. The findings of the functional studies are prognostically correct, since the patient's condition is now no worse than it was when she was observed two years ago.

No.	Name	Date	Clinical Diagnosis	Phthalen Per Cent.		Dis- tase d	Albu- min	Urea in 24-hr. Urine Gm.	Cryos- copy (-) <sup>2</sup>	Urea per L. Blood Gm.	Total Non- protein Blood Gm.	Remarks
				1 hr.	2 hr.							
27	S. 30622	4/ 9/13	Myocardial insufficiency; aortic and mitral insuffi- ciency; atherosclerosis	....	....	10	+	5.1	....	....	....	Died three days after tests.
28	B. 30675	5/29/13	Myocarditis; mitral regur- gitation; chronic pas- sive congestion	18	10	0	0	....	....	....	....	Extreme chronic passive conges- tion at autopsy. Kidneys other- wise normal.
29	K. 30655	6/ 5/13	Arteriosclerosis; myocarditis	....	40	2.5	+	....	....	....	....	Broken compensation present at time of test. Lactose 9 hours. Discharged Aug. 8, 1913, improved.
30	J. 30704	5/29/13	Myocardial insufficiency; aortic insufficiency; myo- carditis	23	18	0	+++	....	....	....	....	Died in broken compensation, which was severe at time of all tests. Kidneys showed only chronic passive congestion.
31	B. 30625	4/ 9/13	Myocardial insufficiency; aortic insufficiency; arterio- sclerosis	....	....	10	0	....	....	....	....	Convalescing at time of test. Dis- charged April 13, 1913; condition improved.
32	L. 30618	3/31/13	Myocardial insufficiency...	....	....	1.4	+	3.7	0.54	....	....	Moderate broken compensation at time of test. Discharged June 24, 1913; unimproved.
33	H. 30380	3/ 7/13	Acute endocarditis; acute lobar pneumonia; poly- serositis	....	....	3.3	+	8.1	....	....	....	Patient died without recovering compensation. Autopsy 3545.
34	J. 30461	3/ 7/13	Myocardial insufficiency; aortic and mitral insuffi- ciency	....	....	10	+	19.3	0.56	0.355	....	Broken compensation at time of test. Discharged April 3, 1913, improved.
35	E. 30608	2/25/13	Myocardial insufficiency; aortic and mitral insuffi- ciency	29	25	3.3	++	10.2	0.48	0.108	....	Severe broken compensation; death without recovery. Kidneys nor- mal at autopsy except chronic passive congestion.
36	C. 30175	1/18/13	Myocardial insufficiency; pericarditis; myocarditis	....	....	2.5	+	....	0.56	....	....	Died. Kidneys normal at autopsy. 3870.
37	A. 30201	1/17/13	Myocarditis .....	36	19	1.7	+	....	0.67	....	0.470	Autopsy: Chronic passive conges- tion; myocarditis. Kidneys other- wise normal. 3838.
38	K. 30502	5/ 2/13	Myocardial insufficiency; mitral insufficiency; arterio- sclerosis	16	17	0	+	13.4	....	....	....	Died May 3, 1913.
39	M. 30603	3/ 7/13	Myocardial insufficiency; arterio- aortic insufficiency; arterio- sclerosis	....	....	0	±	8.6	0.53	0.432	....	Guaiac +. Discharged March 28, 1913, improved.
40	H. 30666	3/10/13	Myocardial insufficiency; arteriosclerosis	....	....	2.5	-	13.4	....	....	....	In broken compensation at time of test. Discharged May 13, 1913, improved.
41	G. 30492	3/ 7/13	Mitral stenosis; mitral in- sufficiency; hemiplegia	....	....	2.3	±	36.7	...	...	....	Severe broken compensation at time of test. Died. Kidneys nor- mal except for chronic passive congestion.

and normal diastatic activity. The rapid increase in the total non-protein N in Case 20, reaching 2 gm. per L. just prior to death, is also worthy of note.

No serious disagreement in the findings of the various tests in this group is encountered, except that diastatic activity is normal in two cases of severe nephritis which show cumulative phenomena.

In considering diastase as an index of the functional capacity of the kidney in uncomplicated nephritis, it is evident that in the majority of instances it is of some value. In three cases of mild nephritis, however, severe involvement of function has been indicated where the other tests and the clinical history fail to substantiate this, while in two cases of severe nephritis with very low phthalein output and with cumulative phenomena, no decrease at all in functional capacity is indicated. Since its findings are entirely out of harmony in five cases in a series of twenty-six, obviously no absolute reliance can be placed in it. The test must be considered of only corroborative<sup>10</sup> value.

*Group C—Cardiac Cases.*—Fifteen cardiac cases, myocardial insufficiency, endocarditis, etc., unassociated with nephritis were studied, eight of them coming to necropsy. As previously pointed out, these cases rarely have the markedly decreased phthalein output which is seen in severe grades of nephritis, although they may present a similar clinical picture. Only when the passive congestion is of an extreme grade is the phthalein output much reduced. With restoration of compensation, the phthalein rapidly becomes normal again. Of the six cases in which the phthalein output was studied, five patients died. Two had more than a 50 per cent. output, two 40 per cent., one 33 and one 28 per cent. In severe myocardial breaks there is some tendency to a reduction of the output for the first hour (the highest output for the first hour was 36 per cent.), with a fair output the second hour. In many instances the outputs for the first and second hours are nearly equal. In this condition the first hour excretion is often a truer index to function than that for two hours.

Diastase determinations were made in all these cases. Three patients died with a perfectly normal diastatic activity, although two of these had earlier showed a decreased content. Four others died with a fair activity, two with a zero output, while two did not die, although the diastase was very low—zero in one instance. Therefore, little dependence, prognostically or diagnostically, can be placed on the diastase findings.

As has been previously pointed out by Strauss and Hohlweg, marked increase in blood urea and total non-protein N is not fre-

10. Where the findings of the diastase test conflict with those of the phthalein, blood urea or blood nitrogen, we would discard the former.



TABLE 4. Group D. CARDIO-RENAL CASES

No.	Name	Date	Clinical Diagnosis	Phthalate Per Cent.		Dis- tase d	Albu- min	Urea In 24-hr. Urine (gm.)	Cryos- copy (-)	Urea per L. Blood (gm.)	Total Non- protein Blood (gm.)	Remarks
				1 hr.	2 hr.	39						
42	Z. 31821	12/12/13	Chronic nephritis; myocar- dial insufficiency	60	13	2.5	++	....	....	....	0.320	Discharged Dec. 13, 1913, improved.
43	J. 31049	2/25/13	....	....	....	3.3	+	15.9	0.57	0.480	....	Mild broken compensation at time of test. Discharged March 14, 1913, improved.
44	B. 30117	3/7/13	Myocardial insufficiency; aortic and mitral insuffi- ciency; chronic nephritis	21	5	5	+	....	....	....	0.320	In broken compensation at time of test. Discharged Feb. 19, 1913, convalescent at time of test.
45	G. 31557	1/3/13	Myocardial insufficiency;	51	15	20	+	....	0.56	....	0.340	In broken compensation at time of test. Discharged April 9, 1913, improved.
46	B. 30599	3/23/13	Myocardial insufficiency; chronic nephritis	30	13	2.5	++	20.1	....	....	0.650	In broken compensation at time of test. Died.
47	J. 30482	3/12/13	Myocardial insufficiency; hemiplegia; chronic neph- ritis	40	18	5	+	30.2	....	....	0.390	Fair compensation at time of test.
48	S. ....	5/29/13	Myocardial insufficiency; mitral insufficiency; arterio- sclerosis; chronic nephritis	12	45	0	....	....	....	....	....	Discharged Mar. 21, 1913, improved.
49	B. 31084	3/7/13	Myocardial insufficiency;	44	11	5	+	19.8	0.59	0.280	0.280	In moderate broken compensation at time of test. Discharged May 5, 1913, improved.
50	S. 30652	4/9/13	Chronic nephritis; aortic insufficiency; arterio- sclerosis; chronic nephritis	40	17	1.3	--	19.8	0.60	0.460	....	In moderate broken compensation at time of test. Discharged April 11, 1913, improved.
51	C. 30679	4/9/13	Myocardial insufficiency; arterio-sclerosis; chronic nephritis	....	....	9	+	6.3	....	....	....	Chronic passive congestion of kid- neys; otherwise normal at au- topsy. 3866.
52	G. 30554	4/2/13	Myocardial insufficiency; myocarditis; acute endo- carditis; chronic diffuse nephritis	....	....	0	+	19.4	0.50	1.100	....	In broken compensation at time of test. Discharged May 28, 1913, improved.
53	G. 30658	4/2/13	Myocardial insufficiency; arterio-sclerosis; chronic nephritis	....	....	0	+	19.1	0.55	0.650	....	Discharged Mar. 30, 1913, improved.
54	J. 30580	3/26/13	Myocardial insufficiency	....	....	5	++	....	....	....	....	Discharged Dec. 30, 1913, improved.
55	J. 31706	12/18/13	Myocardial insufficiency;	....	60	10	±	....	....	0.300	0.322	Discharged Dec. 10, 1913, improved.
56	R. 31752	11/27/13	Myocardial insufficiency; chronic nephritis	48	30	2.5	+	....	....	....	0.518	

quently seen<sup>11</sup> in pure passive congestion. A cumulative phenomenon is only seen once in six cases in which such studies were made, e. g., Case 37 in which the freezing point was  $-0.67$  and total incoagulable nitrogen on the upper limit of normal, .47 gm. per L.

*Group D—Cardiorenal Cases.*—Fifteen cases fell into this group, three of which ended fatally. The relative and absolute degree of cardiac and renal involvement varied much in the different cases, so that practically all types of cardiorenal cases are included.

One patient (No. 47) died showing a normal diastase during a cardiac break in nephritis. The phthalein here was 40 per cent. first hour and 18 per cent. second hour. Two patients (Nos. 52 and 53) died with a zero output and one of these showed only a chronic passive congestion at necropsy. Two (Nos. 48 and 51) left the hospital improved after exhibiting a zero output. In six cases a normal diastase was encountered, but in three of these the renal function was good as indicated by the other tests.

It has been previously pointed out that diseases of the kidney may be clinically identical, but functionally and pathologically different, and that by the aid of the phthalein test it is possible to determine in any given cardiorenal case whether the heart or the kidney is relatively more responsible for the clinical picture presented. This is not possible by the diastase test, since the diastatic activity seems to be markedly but inconstantly depressed in both cardiac and renal disease.

Cumulative phenomena were encountered in only three cases, all of which died. Case 52 is of special interest as the necropsy showed no changes other than passive congestion, although the blood urea was 1.1 gm. per L. The freezing point was at the same time not at all depressed.

*Influence of Blood and of Albumin on Diastatic Activity.*<sup>12</sup>—In the foregoing table blood is recorded in the urine in seven instances. In the other cases microscopical examination or the guaiac test failed to show its presence. Three cases of mild nephritis showed blood and a normal or high "d." A mild nephritic on two occasions showed a low "d," one severe nephritic and one cardiac case a zero "d" value in the

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11. We have now seen three cases in which cumulative phenomena have been encountered in pure chronic congestion, e. g., Cases 37 and 52 and a third case which has been reported by Marshall and Davis.

12. As stated above, this test deals only with "diastatic activity" and not with "diastase content." The activity is dependent on environment and not on actual amount of diastase. Only the influence of albumin and blood have been considered here, since they have entered into the interpretation of the findings of the test in the hands of certain authors.

presence of blood. According to Wohlgemuth<sup>13</sup> and to Corbett,<sup>14</sup> blood accelerates diastatic activity.

Wohlgemuth<sup>15</sup> and Neumann<sup>16</sup> do not consider that the presence of albumin affects the diastatic activity of the urine, while Corbett and Geyelin<sup>17</sup> think that it may, claiming that higher findings are encountered in cases with marked albuminuria.

In the sixty diastase determinations made, the presence or absence of albumin was noted in fifty-six instances, with forty-eight positive findings. Exact quantitative studies of the albumin content were not made, the amount present being indicated as a trace, +, ++, etc.

In the twelve cases of mild nephritis six cases showed a normal or high "d" value. In none of these was there much albumin in the urine, but in three the guaiac test was positive. Only once (Case 7) was much albumin present, the "d" value was low, but later with less albumin the "d" sank to 0—blood still persisting in the urine.

In fourteen cases of more severe nephritis much albumin was present in five instances and in two of these a normal "d" was encountered. One of these cases (No. 19) had normal function indicated by all other tests except the salt test, so that it is not necessary to assume that the albumin was responsible for the high "d" value in this instance. In Case 17, despite the presence of large amounts of albumin and the presence of blood, a zero "d" value was present.

In fifteen cardiac cases much albumin was present in three instances and a normal diastase value only once. Case 29 with about the same amounts on each occasion gave a 0 value at first and a normal one later. The patient died. The phthalein here showed definite functional impairment, 23 and 18 per cent. for the first and second hours, respectively—the first hour reading being probably the truer index to the function.

In fifteen cardiorenal cases much albumin was present in four cases and normal diastase once in three of the four cases in which it was determined. In the series of severe renal and cardiorenal cases, twelve instances of marked albuminuria were found and in only four cases was "d" normal or higher, while in four it was 1.7 or 0.

Analysis of our data does not indicate that albumin plays a great rôle in activating diastase. Are we justified, then, in ascribing high or normal values in the presence of marked albuminuria to activation of diastase by the albumin? In Case 19 we have an instance of hyper-

13. Wohlgemuth: *Ztschr. f. Urol.*, 1911, v, 801.

14. Corbett: *Quart. Jour. Med.*, 1913, vi, 365.

15. Wohlgemuth states that with the technic here employed no activation occurs unless the albumin is present in large amount.

16. Neumann: *Deutsch. Arch. f. klin. Med.*, 1913, cxi, 164.

17. Geyelin: *THE ARCHIVES INT. MED.*, 1914, xiii, 96.

permeability of the kidney—high phthalein, 70 per cent. for two hours, normal diastase, normal urea output, no cumulative phenomena but retention of salt. It is not necessary to assume that the diastatic activity has been accelerated by the albumin.

First it seems advisable to determine whether or not albumin does activate diastase, and if it does, to what extent. In case it does, then it must be determined whether the character of the albumin or the quantity plays a rôle and to what extent. Since albuminuria is almost constant in conditions in which the diastatic activity is determined, and since marked albuminuria may be associated with zero and low "d" values, it constitutes a serious defect in the test to attempt to ascribe normal or high findings in certain instances to the presence of albumin. Uncertainty as to the interpretation of the findings of a test must of necessity decrease the practical value of that test.

#### CONCLUSIONS

1. The quantitative estimation of the diastatic activity of the urine as it is employed at present shows low values in the majority of cases of mild and severe nephritis, while in cardiac and cardiorenal cases the diastase findings are bizarre. Owing to the frequent occurrence of normal diastatic values in cases in which considerable or grave renal functional involvement is unquestionably present, and of low diastatic values which are not in accord with the clinical course of the case or with findings of other functional tests, no diagnostic or prognostic significance attaches to this test, other than that which is corroborative in character. As a single test it is unreliable. Further data as to the influence of albumin on the "d" value are desirable.

2. The phthalein test is the one of choice and unquestionably the most valuable single test in this group of cases.

The total non-protein N and urea content of the blood are of about equal value in severe cases, while the freezing point of the serum is probably of somewhat less value since depression in the freezing point is lacking in several instances in which one or both of the other tests indicate that retention is present.

3. Both tests of excretion and of retention are valuable. In all cases a phthalein test is advisable. *Wherever the phthalein output is decreased even but slightly the total non-protein nitrogen or the blood urea or both should be determined.*

# THE EFFECT OF SODIUM SALICYLATE ON VARIOUS TYPES OF EXPERIMENTAL ARTHRITIS\*

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The following experiments were made in order to determine the effect of salicylates in animals inoculated with various types of streptococci. These cocci were isolated from various sources, and their causal relation to certain clinical conditions, especially of the rheumatic types, is pointed out in its appropriate place with the several series of experiments reported below.

The experiments with the different organisms were all carried on in the same way. The animals used were rabbits. They were given, in some cases on the previous day, in other cases from one to two hours previous to inoculation, 5 grains of a synthetic preparation<sup>1</sup> of sodium salicylate subcutaneously or intramuscularly. They were then inoculated intravenously with suitable doses of living suspensions of twenty-four-hour cultures of the streptococci. On each subsequent day from 3 to 5 grains of salicylate were given to the animals, usually subcutaneously, for a period of two to three weeks if the animal lived, or until the animal died. Careful observations of the animals were made from day to day for evidence of infection, especially arthritis. In all experiments a series of six animals were inoculated with identical amounts of culture, three of which received the salicylate as above indicated, and three served as control animals. Young animals were used, since they are more susceptible to infection than old animals.

*Experiment 1.*—Six young rabbits were carefully selected, of approximately the same weight and age and about three-quarters grown. Their weight was about 1.100 gm. All were given, into the ear vein, equal amounts of Streptococcus 236 suspended in about 2 c.c. of salt solution. Three animals had received two hours previously 5 grains of sodium salicylate subcutaneously; this same amount was continued daily following the injection. Streptococcus 236 is an organism that was isolated from a person dying of an infection which began as a sore throat and which occurred during the Chicago milk epidemic in 1912. It was hemolytic and encapsulated and possessed the properties of the epidemic type of streptococci as described by Dr. Rosenow and myself previously.<sup>2</sup> The reasons for testing an organism of this type are readily appar-

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<sup>1</sup> From the Department of Experimental Medicine, University of Illinois, Chicago.

1. It has been shown by Waddell (ARCHIVES INT. MED., 1911, viii, 784) that the synthetic preparations of salicylates behave like the natural products.

2 Davis, D. J., and Rosenow, E. C.: An Epidemic of Sore Throat Due to a Peculiar Streptococcus, Jour. Am. Med. Assn., 1912, lviii, 773.

ent, since the use of salicylates, aspirin, etc., is so universal in cases of severe sore throat, especially when complicated by joint symptoms as not infrequently happens.

In this series all the animals died, each having developed multiple arthritis. The three receiving salicylates lived four, seven and three days, a total of fourteen days following inoculation. The controls lived eight, eleven and seven days, a total of twenty-six days. Two of the former and one of the latter showed slight lesions of endocarditis. From the joints in all the animals the streptococcus was recovered and in four of the six the heart's blood at necropsy yielded streptococci. It is evident from this experiment that the salicylates had no favorable influence on the course of the infection with this streptococcus. Indeed, the data indicate rather a slight unfavorable effect.

*Experiment 2.*—The next series of animals were inoculated with a hemolytic streptococcus of bovine origin isolated from the udder of a cow suffering with severe mastitis. It was very similar to *Streptococcus* 236 and was highly virulent to animals. The experiment was made exactly as was the previous one. All the animals developed multiple arthritis. The three receiving salicylates died after five, two and three days, respectively. Two of the controls died after five and three days and the remaining animal was still alive one month later though suffering from a large and badly deformed joint. One of the salicylate rabbits at necropsy revealed endocarditis. In the heart's blood of the five animals that died streptococci were found post mortem. Here again the salicylates had no favorable effect; if anything the reverse.

*Experiment 3.*—The next series of animals was treated exactly as in the previous experiments except that after the first dose of 5 grains, 3 grains of salicylates were given daily. This of course is still relatively a large dose. The streptococcus used was obtained from Dr. E. C. Rosenow, who shortly before had isolated it from the kneejoint of a person suffering with acute rheumatic fever. This organism had the general properties of the *Diplococcus rheumaticus* as described by Poynton and Payne. Since these organisms are less virulent for animals than the hemolytic streptococci, it was necessary to inject considerably larger doses, the growth from three blood-agar slants being given to each animal. All the animals without exception developed arthritis of greater or less intensity and multiple in character. Only one, an animal which was receiving salicylates, died; this occurred nine days after inoculation and the necropsy revealed multiple acute arthritis, endocarditis and fibrinous pericarditis. Cultures were positive from all these lesions. Three of the animals were killed after eleven days and cultures from joints yielded streptococci. The remaining two animals, one receiving salicylates daily for three weeks, and the other as control, were kept under observation for three months. No appreciable effect of the salicylates was evident. At the end of this time the joints in both animals were still distinctly and about equally enlarged. Otherwise the animals appeared normal and were not emaciated.

*Experiment 4.*—The next series of animals was inoculated with a streptococcus (256) isolated from the tonsil crypts in pure culture from an individual suffering with chronic tonsillitis and chronic rheumatoid arthritis. This organism was probably the causal agent in this condition. It was hemolytic and highly virulent for animals. The experiments were carried on exactly as with the other organisms. All animals developed multiple joint lesions within a few days. Those receiving the salicylates died after five, eight and nine days, respectively. No endocarditis. Two of the control animals died after four and five days; the third animal did not die, but developed multiple arthritis, the lesions becoming chronic and leading to marked enlargement and deformity of some of the joints. In connection with this experiment another rabbit was inoculated with a small dose of the same streptococcus (256). Joint lesions appeared after several days. Seven days after the inoculation and at a time when the arthritis was distinct, the animal was given 5 grains daily of sodium



salicylate. The lesions continued in a chronic state and showed no appreciable improvement after several weeks. The general course of the infection in this animal was almost identical with the outcome in the control animal that lived in the previous experiment, though it had a somewhat smaller dose of streptococci. It must be said, therefore, that the sodium salicylate had no appreciable effect on the course of the infection.

#### SUMMARY

It is clear from the several series of experiments here reported that sodium salicylate does not exert a favorable effect on infections in rabbits caused by various types of streptococci under the conditions detailed above. It does not prevent localization of the organism in joints, nor does it prevent the appearance of endocarditis. It would seem to have, therefore, no prophylactic value, nor does it alter the course of the infection after it has once become established.

## SKIAGRAPHIC STUDY OF THORAX, THORACIC WALL AND THORACIC VISCERA \*

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The Roentgen-ray picture of the normal or abnormal thorax invariably shows certain opacities corresponding to the hilus of the lung. Latent tuberculosis is found in this same location, and it has been stated that tuberculosis always begins here and spreads through the lung in a peripheral direction. It is of prime importance, therefore, to ascertain if possible the cause of these opacities.

An attempt was made to analyze the roentgenogram of the thorax by taking a cadaver and making a Roentgen-ray plate of the thorax intact; of the thorax with heart and lungs removed; of the posterior thoracic wall alone; of the detached heart and lungs; of the heart separate; of the lungs freed from the heart and vessels, and finally of the lungs with the bronchi, artery, or vein injected with opaque emulsion of barium sulphate, or with citrated blood.

The cadaver was that of a negress, aged about 65, who died of gangrene of the legs due to extreme anasarca, probably of renal origin. No physical or other examination of the lung was made prior to death.

The roentgenogram of the intact thorax showed an enormous heart shadow. This roentgenogram was made with the subject lying on the back, the plate underneath and the tube 26 inches above the plate.

The roentgenogram of the intact thorax does not show quite so many opacities as usual beside the heart, because the heart shadow overlaps and obscures them. Nevertheless, a few opacities appear in the region of the hilus of the lung. A careful dissection later showed complete absence of calcified lymph-nodes; the numerous peribronchial lymph-nodes were pea-sized and of a dark, almost black, color. In Figure 2 the costosternal cartilages are seen, just to the right of the sternum. It is impossible to trace these cartilages throughout their extent, and hence they may at times cause shadows that might be mistaken for shadows of something else, as for instance, calcified nodes.

The lower lobe of the right lung shows an infiltrated condition, which was evidenced in the gross specimen by a sharply demarcated zone of deep red in contrast with the pale color of the normal lung

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\* From the Pathological Laboratory, Austin Presbyterian Sanitarium.

above. This infiltration shows beautifully in Figure 6. It was easily detected by palpation of the specimen, as the lung was less crepitant in the affected region. The roentgenogram of the intact thorax gives only a hint of this condition. The failure to show this might be attributed to the fact that the tube was not centered directly over the region, and might suggest that an intensive study of the lung could be better made by a series of small roentgenograms made with the tube in each instance accurately centered over the area in question.



Fig. 1.—Intact thorax; picture made post mortem. Note the mottling seen in some of the intercostal spaces, especially on right side, low down. Heart is large, apex projecting beyond edge of plate.

The picture of this thorax does not show the bronchovascular tree, probably because the heart and pericardium overshadows the portion where the tree should show plainest, and because of the post mortem collapse of the vessels.

A comparison of Figure 2 with Figure 1 shows that practically all the opacities are due to the contents of the thorax and not to the thoracic wall. The single exception is the shadow due to the costosternal cartilages referred to above, and which is visible in Figure 2. The blood-vessels and lymph-nodes of the chest wall do not show at

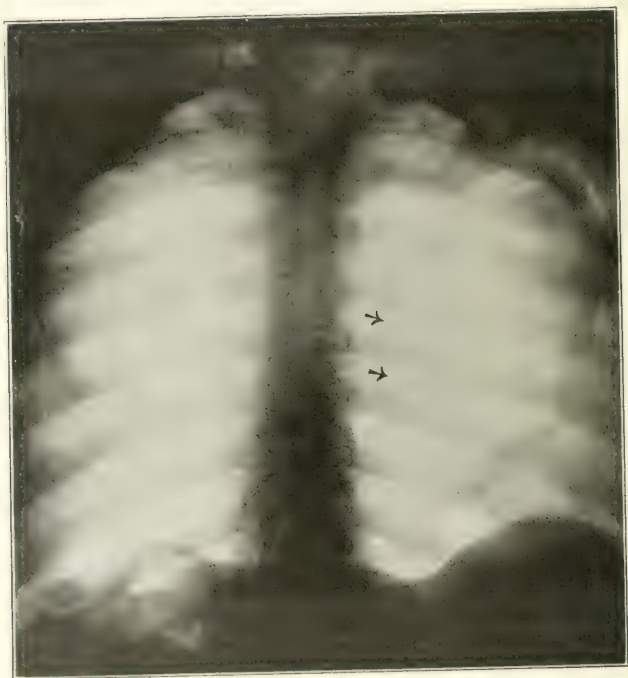


Fig. 2.—Front and back thoracic wall with lungs and heart removed. Note absence of densities or obscurities in interspaces. Intercostal cartilages show very faintly near arrows.

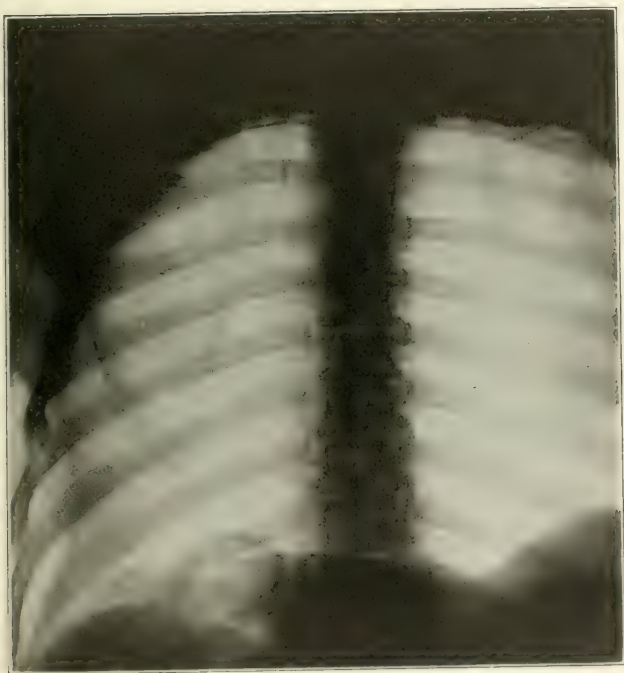


Fig. 3.—Posterior thoracic wall alone. Intercostal cartilages absent.

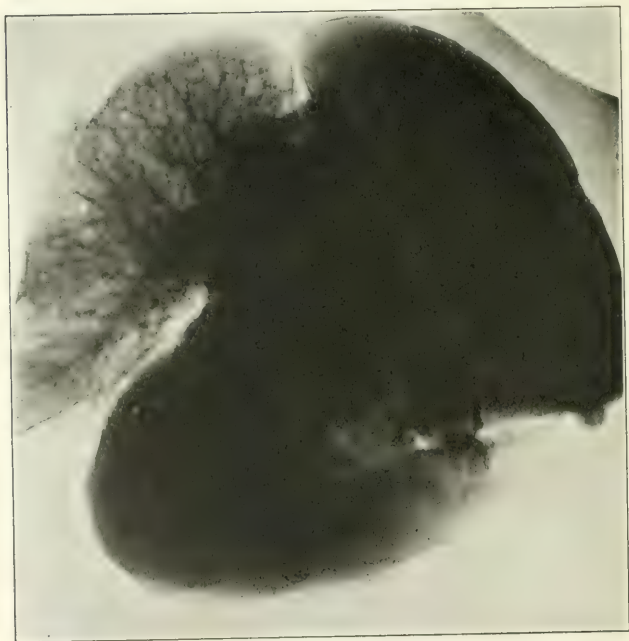


Fig. 4.—Heart and lungs after removal. Note consolidation of lower lobe of right lung. Hilus shadow shows on left side. Note the arborization of lung by bronchi and vessels.





Fig. 5.—Heart and part of great vessels. Note that the heart, connective tissue, and vessels all obstruct the Roentgen rays.

all. Figure 3 is the equivalent of Figure 2, except that the anterior thoracic wall has been removed.

Figure 4 is instructive in that it shows many dense areas in the region of the hilus. These shadows are not due to lymph-nodes, because dissection proved that none of the nodes were calcified. It is difficult to account for all these densities on the ground that they are shadows of bronchi, because the bronchi (as will be noted later in this article) show as pairs of parallel lines with a rarefied area between. Certain it is that the bronchi do not satisfactorily account for all the hilus area. A part of the hilus density is evidently due to blood vessels, pericardium, mediastinal fat, and adventitious connective tissue.

Figure 5 presents all the densities and opacities due to the fibrous connective tissue in and around the arteries, veins and heart. Figure 5 stands in marked contrast to Figure 6, because the latter showing the lungs alone is comparatively free from densities and opacities. It seems that the contrast between the roentgenogram of the lungs alone (Fig. 6) and that of the heart and vessels (Fig. 5) brings out a valuable lesson, namely, that hilus shadows are due not only to the bronchi, but also to the blood vessels, and adventitious connective tissue.

Our studies were continued with lungs from healthy sheep. These organs are very similar to human lungs but differ in one rather important particular; namely, they have thin-walled bronchi with relatively large lumen. The density of bronchial shadows as compared with that of blood vessel shadows is brought out in Figures 7 and 8. The first of these shows sheep lungs and heart intact. The second (Fig. 8) shows sheep lungs with the heart removed while the blood-vessels and other little tags of mediastinal tissue remain. Note how much the picture is cleared up when the lungs are freed from the vessels (as far as possible). Figure 9 represents the lungs of the sheep after all blood-vessels and tags of mediastinal tissue are removed from the hilus. The minute density near the lower border of the left lung (seen better in Figures 8 and 10) is a calcified area, verified by actual dissection. Its occurrence in this sheep, selected at random, indicates that calcified areas are not uncommon, especially since we have found them in about 5 per cent. of human chests examined. We do not consider a dense area as necessarily a calcified area unless it is clearly defined and isolated.

The appearance of the heart and lungs in Figures 4 and 7 is in one respect unnatural, namely, in so far as heart and vessels are practically empty. It can be observed in these two pictures that the blood-vessels do not cast a distinct shadow. The blood content is lacking. Figure 11 and Figure 12 show the difference between the shadow cast by the pulmonary artery when empty and when distended



Fig. 6.—Lungs freed from heart and vessels. The probes are in arteries and veins, but these are collapsed and do not show. Note above all that each bronchus shows as two parallel dark lines with a light band between. Note the consolidated lower right lobe.



Fig. 7.—Heart and lungs of sheep.



Fig. 8.—Same as Figure 7, except heart has been cut away, leaving great vessels, of which the mouths show as rings.



Fig. 9.—This is same as Figure 8, except that vessels are, as far as possible, cut away. Note absence of obscure hilus densities.





Fig. 10.—Same as Figure 9, but now injected with barium emulsion. The small lobe, bronchus alone injected. Large lobe on same side, artery alone injected. Large lobe on opposite side, vein alone injected. Note that the vessels accompany the bronchi and are of about the same size.



Fig. 11.—Sheep heart and lungs with vessels empty and collapsed; needles inserted ready to inject citrated blood.

by blood. The artery with its column of blood casts a distinct shadow in Figure 12. The relative position of all structures is identical in the two pictures, because the needle for injecting the blood was *in situ* before Figure 11 was made. Immediately after exposing the plate for Figure 11 the clamps were released and citrated blood was allowed to



Fig. 12.—Same as Figure 11, except clamps were released and citrated blood was allowed to run in without moving specimen, which is in almost exactly the same position as shown in Figure 11. Note the pulmonary artery shadow accompanying the primary bronchi. The arrow points to a branch of the pulmonary artery going to small upper lobe.

run into the pulmonary artery under six feet gravity pressure. Note that the artery with its contained blood casts a dense shadow, whereas the accompanying bronchi show negatively as vacuities except that the side walls of the bronchi seen in section show as a density.

Figure 13 shows the difference in the roentgenogram of a bronchus and that of an artery of about the same size. The artery is full of blood. It will be observed that the bronchus shows as a light streak (lumen) bordered by a dark streak (wall) on each side. The blood-vessel, however, shows as a uniformly dark band, except for the fact that in this instance an air bubble shows as a round light area.

None of the plates have been retouched, and the half-tones do not give an absolutely perfect idea of all the points.

#### CONCLUSIONS

1. The anterior and posterior chest walls offer no source of error in interpreting hilus shadows, except that the costal cartilages may be



Fig. 13.—Artery and bronchus. Note difference in character of shadow cast. The artery is distended by citrated blood. Note air bubble in artery.

irregularly calcified; this condition is easily recognizable in the roentgenogram.

2. When the lung and heart are removed from the thorax and roentgenograms made, it is clearly seen that all the obscure densities in the thoracic roentgenogram are of visceral origin.

3. The vessels and adventitious connective tissue cast distinct shadows on the roentgenogram.

4. The shadows cast by the bronchi are linear and do not easily fuse to form a broad shadow such as that seen ordinarily in the hilus

region. On the other hand, the shadows of blood-vessels are uniform, and when filled with blood might easily fuse to form the greater part of the hilus shadow.

5. The lumen of the bronchus more than compensates for the fibrous tissue in its wall, so that the bronchial shadow consists (on the negative) of a dark band bounded by two narrow light bands, the latter being due to the bronchial wall in section.

6. The vessels correspond to the bronchi and are distributed in a similar manner throughout the lung, except the first one or two subdivisions at the hilus.

7. The hilus shadow is not due to lymph-nodes, although in some cases of disease these might participate in its formation.

Note: After writing the foregoing we discovered a reference to similar work done earlier by Dunham, Boardman and Wolman, who conclude that the hilus shadow is due jointly to bronchi and vessels; also work by Fraenkel and Lorez, who attribute the entire hilus shadow to the vessels, especially the pulmonary artery; and work by Sewell and Childs, who like us, believe that the hilus shadow is almost entirely due to the vessels.

No reference was made to any injections of citrated blood. For this reason, and also for the reason that the workers mentioned did not perfectly agree among themselves, the present report is published.

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3. Fraenkel, E., and Lorez, A.: *The Anatomical Meaning of the Hilus Shadow in the Skiagram of the Chest*, *Arch. Roentgen Ray*, 1910, xiv, 288.
4. Sewell, H., and Childs, S. B.: *A Comparison of Physical Signs and X-Ray Pictures of the Chest in Early Stages of Tuberculosis*, *THE ARCHIVES INT. MED.*, 1912, x, 45.

## METASTATIC CALCIFICATION\*

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Metastatic calcification would seem to be a rare condition, if estimated by the number of cases reported in the literature, but it is undoubtedly often overlooked, and many cases that are recognized are probably not recorded. In 1911 I was able to collect from the literature but twenty-nine cases,<sup>1</sup> and since that time there have been but two more cases recorded (those of M. B. Schmidt<sup>2</sup> and Schober<sup>3</sup>) so far as I can find. The small number of cases published, and especially the important bearing this condition of metastatic calcification has on the general problems of calcium metabolism, ossification and pathological calcification, makes each additional case worthy of study and report.

By metastatic calcification is implied that the wide-spread deposition of calcium salts is a result of their excessive absorption from the normal depots, and excludes instances in which wide-spread tissue injury is the primary cause of a deposition of calcium salts. As Virchow inferred when describing this condition originally, it is a result of oversaturation of the blood with calcium salts. This view has received almost unanimous acceptance because it was found that metastatic calcification usually accompanied extensive destruction of bone tissue (for instance, tuberculosis or neoplasms of bones, and leukemia), which would result in the absorption of considerable amounts of the bone salts. This explanation received experimental support from Tanaka,<sup>4</sup> who injected soluble calcium salts into the peritoneal cavity of animals and found not only local deposits of calcium, but also deposits in remote tissues; his work has been corroborated by Katase,<sup>5</sup> who obtained the same results also by subcutaneous and intravenous injections.

One of the striking features of metastatic calcification as observed in human pathology is the predilection of the lungs, stomach and kidneys as the site of deposit. As the deposit, contrary to the rule in ordinary pathological calcification, takes place in tissues not previously

\* Submitted for publication Oct. 16, 1914.

\* From the Department of Pathology, University of Chicago.

2. Schmidt, M. B.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 59.

3. Schober: *Inaugural Dissertation*, Breslau, 1914; quoted by Stumpf, *Centralbl. allg. Pathol.*, 1914, xxv, 801.

4. Tanaka: *Biochem. Ztschr.*, 1911, xxxv, 113.

5. Katase: *Beitr. pathol. Anat. (Ziegler's)*, 1914, lvii, 516.

1. Wells, H. G.: *THE ARCHIVES INT. MED.*, 1911, vii, 721.



injured or altered, and as these three organs are not often the site of calcification independent of local lesions, their selection is striking. The explanation would seem to lie in the fact that in these tissues we have the three chief places in the body where acids are excreted, and where, in consequence, the fluids must be most alkaline. An especially conclusive bit of evidence of the correctness of this hypothesis is furnished by metastatic calcification in the stomach, where, as pointed out by Hofmeister,<sup>6</sup> the deposits are limited to the interglandular tissue about the upper part of the glands of the fundus, that is, exactly corresponding to the location of the acid-secreting parietal cells.

In another place<sup>1</sup> I have pointed out the important part played by the carbon dioxid of the blood and tissue fluids in the transportation, absorption and deposition of calcium salts. Metastatic calcification provides a striking demonstration of this fact, not only by the marked and almost invariable calcification of the alveolar walls of the lung where the carbon dioxid is given off from the blood, but especially by those cases in which there is found also an extensive deposition of lime salts in the pulmonary veins, the left side of the heart, and the systemic arteries, that is, where the blood is poorest in carbon dioxid. Among such cases are the following:

Lazarus and Davidsohn<sup>7</sup> found in a 19-year-old girl with sarcoma of the dura eroding the skull, resulting in extensive metastatic calcification, a marked calcification of the intima of the left auricle, without involvement of the muscle itself. There was no calcification of the left ventricle or in the large pulmonary arteries and veins, and but a single calcified plaque in the aorta. It is particularly noted that the calcium has been deposited from the lumen of the auricle directly into the adjacent endocardium, supporting the hypothesis that the existing condition is the result of oversaturation with calcium from the blood in the left auricle.

Versé<sup>8</sup> described a case of myelogenous leukemia in a 25-year-old laborer, in which there was metastatic calcification that was especially marked in the lungs and left auricle. The latter is described as follows: The entire intima was white, except here and there some gray stripes and lines in places that were not calcified. The calcification ceased at the orifices of the pulmonary veins, extended down to the mitral ring and extended somewhat into the auricular appendix. The musculature of the heart was free from calcification. In the pulmonary artery there were only a few small yellow thickenings, but in the abdominal aorta were larger plaques with calcification, and also the media of the arteries of the lower extremities was much calcified. The lung contained numerous areas of calcification of the alveolar walls, and the pulmonary veins were heavily calcified with large rigid plaques. The deposits gave reactions for carbonates and phosphates. Microscopically the pulmonary veins showed the calcification to involve the media, but with the elastic fibers well preserved. In the auricle the deposits occupied the endocardial and subendocardial connective tissues, reaching to but not involving the muscle; here also the elastic fibers were not destroyed except in the oldest areas. In the kidneys the calcification was limited to a few areas in the cortex.

6. Hofmeister: *Ergebn. d. Physiol.*, 1910, ix, 429.

7. Lazarus and Davidsohn: *Ztschr. f. klin. Med.*, 1906, lx, 314.

8. Versé: *Verhandl. d. deutsch. path. Gesellsch.*, 1910, xiv, 281.

M. B. Schmidt's<sup>2</sup> case is one of general calcification without bone destruction, and therefore not entirely within the strict interpretation of "metastatic calcification." Schmidt himself calls it *Kalkgicht*. Advanced nephritis was present in this as in most of the other cases of this sort, and is considered responsible, although the correctness of this assumption is questionable in view of the fact that the kidneys normally excrete but a small fraction of the calcium, most of which is eliminated through the bowels. There was an extensive calcification of the myocardium of the left ventricle, which contained 2.32 per cent. calcium oxid. It was especially located beneath the pericardium, and no mention is made of the condition of the left auricle. There was calcification in the lungs, kidneys, pulmonary veins, stomach, and especially in the systemic arteries. In some of the vessels there were free precipitates of lime salts independent of thrombi or infiltration of the vessel walls, which seem evidence that the deposition has been the result of an oversaturation of the blood with the salts.

It is interesting, also, to go back to the report of Küttner<sup>9</sup> in 1872 of a case of extensive bone disease with extreme calcification of all the systemic arteries, for this observation led Küttner to suggest for the first time the possible importance of the poverty of carbon dioxid in the arterial blood as the explanation of this particular localization, as well as the common occurrence of metastatic calcification in the lungs. In this case, however, there was no involvement of the heart recorded, so it does not fall into the group under discussion.

That calcification of the left auricle is common in metastatic calcification would seem probable, for we find it occasionally mentioned incidentally without particular attention being given to it. For example, Jadassohn,<sup>10</sup> in reporting a case of metastatic calcification resulting from osteomyelitis, merely mentions the presence in the endocardium of the left auricle of several hard white platelets, and of calcification of the papillary muscles and the large vessels in the lungs, but discusses chiefly the concomitant calcification of the skin. Also, in Schober's<sup>3</sup> case there was extensive calcification in the left auricle. Probably this endocardial and intimal localization has been overlooked or not mentioned by several of the observers of cases of metastatic calcification.

A case of typical metastatic calcification in myelogenous leukemia, with extensive involvement of the left side of the heart, thus resembling Versé's case, recently came under my observation in the necropsy room of the Cook County Hospital.

The patient was a Bulgarian laborer, 30 years old, who had a typical myelogenous leukemia of unknown duration. From the necropsy record, which shows the usual findings of myelogenous leukemia, the following points are extracted:

The heart was slightly increased in size by thickening of the left ventricle. There were a few small yellowish subpericardial areas which were not evidently calcified, but the coronary arteries showed extensive calcification. The foramen ovale was open, but protected by a valve-like flap, near which in the left auricle was a calcified plaque. Several other delicate calcific deposits appeared in the endocardium of the left auricle, involving about two-thirds of its entire

9. Küttner: Virchow's Arch. f. path. Anat., 1872, lv, 521.

10. Jadassohn: Arch. f. Dermatol., 1910, c, 317.

surface. Nothing of the kind could be found in the right auricle or ventricle, or in the pulmonary arteries. In the left ventricle under the endocardium there were light colored, irregular streaks and areas in the myocardium which grated when scraped with the knife. These calcified areas were quite numerous and distributed everywhere throughout the left ventricle, most numerous in the septum; but there were no such deposits found in the right ventricle.

The lungs did not collapse, showed a diffuse increase in consistency, and were somewhat dark in color. The cut surface was dry, slightly brownish, and semi-solidified. There was a slight grating sensation on cutting, and a sandy feel to some areas, especially where vessels were cut across.

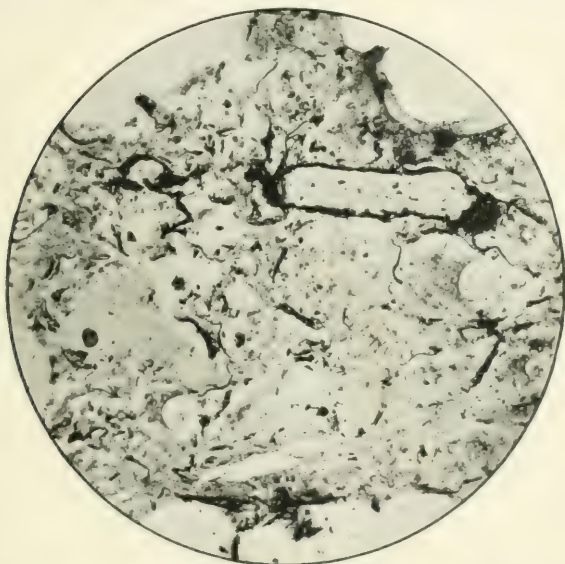


Fig. 1.—Lung, fixed in alcohol and stained by von Kossa's method with silver nitrate. The black-stained phosphate deposits are seen especially in the walls of two pulmonary veins, whereas a section of an artery nearby is not brought out because of the lack of calcification. The discontinuous calcium deposits in the alveolar walls are also well shown. Magnified 75 diameters.

All the other viscera showed the changes usual in leukemia, there being a marked leukemic infiltration of the liver and kidneys, without fibrotic changes in either. The marrow of the sternum and clavicle showed a marked hyperplasia, with destruction of bone tissue; in the sternum there were several well-defined yellow areas in the marrow. Other bones could not be examined, except the calvarium, which seemed to be normal.

No gross evidence of calcification was observed in the stomach or elsewhere in the alimentary tract. The blood-vessels in general were not calcified or sclerotic, this including the vessels of the brain.

Samples of lung tissue and heart muscle were preserved in alcohol. Unfortunately, the other tissues were preserved in Zenker's fluid containing acetic acid, and none of the stomach was kept.

Histological examination of the viscera in general showed only the usual changes of leukemia, there being no calcification demonstrable in Zenker's fixed tissues except in the lungs, myocardium and kidneys. Examination of alcohol-fixed tissues showed the following changes:

*Lung* (Fig. 1).—The heaviest deposits are in the large veins, occurring as thick, rather homogeneous masses which lie beneath the intima and often occupy

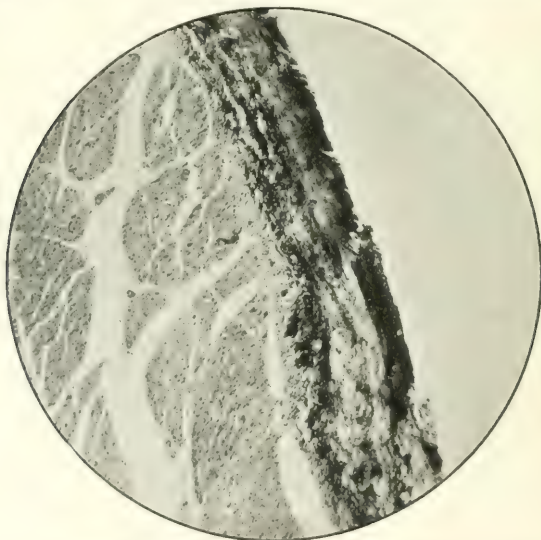


Fig. 2.—Left auricle. Stained by hematoxylin and eosin. The heavy deposit of calcium in the endocardium is shown without involvement of the underlying muscle. This illustrates the fact that the deposition comes from the blood passing through the left auricle. Magnified 52 diameters.

the entire media. The intima itself does not seem to contain any calcium. About some of the veins there is a heavy deposit in the adjacent alveoli, some of which are greatly thickened by masses of hematoxylin-stained homogeneous material. The adventitia of the vessels is not affected. Some of the larger bronchi show a heavy deposit, which is especially marked in the basement membrane beneath the epithelium, although in some places the muscularis is also involved. This finding is of interest in connection with Katase's statement that calcium is excreted through the bronchial mucosa. There is considerable calcification of the bronchial cartilages. The pulmonary arteries show no calcification and form a striking contrast to the adjacent calcified veins. In the alveolar walls there is considerable calcification, involving to a greater or less extent

nearly all the alveoli examined. Here the deposit occurs in a hyaline matrix, apparently formed by the basement membrane beneath the alveolar epithelium, and appears in the form of platelets or rods and scales. In addition to the calcification and a slight leukemic infiltration, there is a marked accumulation of pigmented, typical *Herzfehlerzellen*.

*Left Auricle* (Fig. 2).—Under the intima is a heavy layer of calcium salts, which is, however, discontinuous. It is deposited in narrow bands, which seem to correspond to fibers of the intimal tissue. In places where the process is early, at the margins of the densely calcified areas, it seems to be definitely beginning as a deposit in the elastic fibers, which are picked out as by a selective

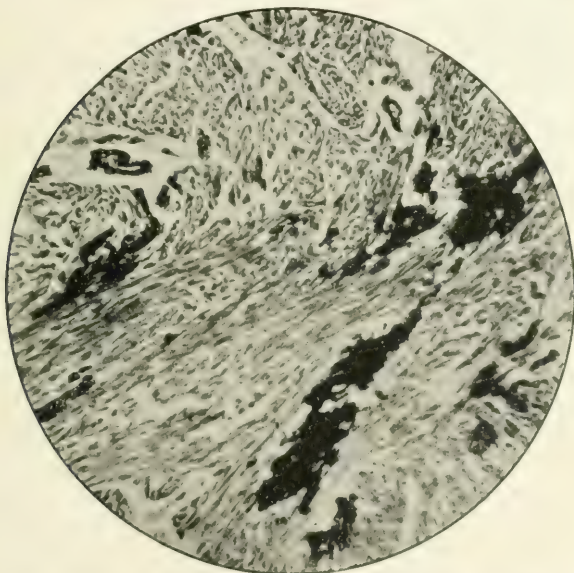


Fig. 3.—Left ventricle. Stained with silver nitrate, showing the heavy deposits in the intima of the small branches of the coronary arteries, and also the heavy deposits within the muscles themselves. Magnified 60 diameters.

stain. It extends down to and in places slightly invades the muscular fibers where there seems to be some proliferative reaction to the deposits. The small arteries also show heavy deposits in the intima, which in some places slightly invade the media. There are no evidences of myocarditis or endarteritis outside the calcified areas; no deposits in the vein walls. A sympathetic ganglion in the pericardium shows no changes.

*Left Ventricle* (Fig. 3).—The heaviest deposits are again in the endocardium, where considerable areas show dense masses of calcium, often extending down into the underlying muscle. The arteries nearly all show heavy deposits in the intima, which usually is unaltered in all other respects; a few of the larger arteries show some proliferation of the intima where not calcified. Deep in



the myocardium are also calcium deposits, which are usually located in the vicinity of small arteries. Here the deposit is in the muscle fibers themselves, in early stages being in the form of small granules, in the later stages so dense that the structures are obliterated, sometimes with transverse lines of calcium, and often with fragmentation of the muscle fibers. In most instances there is no evidence that there has been any preceding change in the muscle fibers, but in some areas there is a concomitant local fibrosis, which might, however, be secondary to the calcification. There are no areas of leukemic infiltration. A large artery shows calcification selectively in the elastic lamina, with also a heavy deposit in the adventitia and in some foci in the media.

When the calcium is removed with acid and the section stained with hematoxylin and eosin, the muscle fibers that were calcified are found to be homogeneous, fragmented, but often with intact nuclei.

*Kidney.*—Besides extensive leukemic infiltration, there are numerous tubules showing calcification of their epithelium, and others showing calcified masses in the lumen. The glomerules and arteries are not calcified.

As the other tissues were not preserved in alcohol, but in Zenker's fluid, which dissolves out small deposits of calcium, we cannot be sure whether there was calcification in them or not. Nothing was found in the Zenker-fixed tissues that suggested the existence of calcification previously.

Sections through the sternum show the usual features of bone marrow in myelogenous leukemia, including an active destruction of the bone tissue.

Sections of the calcified tissues stained by von Kossa's silver nitrate method gave good selective staining of the deposits, showing that phosphates were present. Sections treated with hydrochloric acid gave a slight effervescence of gas showing the presence of carbonates. When treated with sulphuric acid the typical crystals of calcium sulphate were formed.

To recapitulate, we have here a typical case of metastatic calcification, resulting from bone destruction in myelogenous leukemia, making the thirty-second case of metastatic calcification found recorded. Of particular prominence and significance in this case are the heavy calcium deposits in the endocardium of the left side of the heart, the intima of the pulmonary veins and of the cardiac arteries, which illustrates as by a natural experiment the importance of the carbon dioxide of the blood in the transportation of calcium. When bone tissue is being rapidly absorbed, the venous blood becomes loaded with a greater amount of calcium (probably in the form of tribasic calcium carbonate<sup>1</sup>) than arterial blood can hold in solution. Hence in this case of metastatic calcification no calcium is found in the right side of the heart or in the pulmonary arteries, but when the blood has passed through the lungs and lost a large part of its carbon dioxide, the calcium salts are precipitated in the pulmonary veins, the left heart and the arteries and taken up by the adjacent tissues.



## STUDIES IN PANCREATIC DISEASE\*

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### *PART I.—DUODENAL CONTENT ANALYSES AS AN INDEX OF DISEASE, AND FUNCTIONAL ACTIVITY OF THE PANCREAS*

A reliable method for ascertaining the functional activity of the pancreas, has been eagerly sought for the last few decades, in fact since the time that Kuntzman, Richard Bright and Claude Bernard first called attention to this gland as a possible focus of disease.

The large variety of tests offered, some ten to twenty in number, is in itself testimony to the fact that no one test has met the mark or has satisfied the rigorous requirements of both pathologist and clinician. These tests fall into three groups: tests of the external secretion of the pancreas, usually carried out on the stool (Fuld-Gross), the urine (Wolgemuth), or gastric contents (Volhard oil test); tests of the internal secretion, consisting of tests for glycosuria, the Cammidge reaction, the Loewi pupillary dilatation test, etc.; and finally metabolism studies on the absorption of fat, nitrogen, etc., from the intestinal tract.

A detailed criticism of these many tests at this moment would be a large task, and one requiring unnecessary repetition of most valuable and thorough critical studies on the part of Frank,<sup>1</sup> Albu,<sup>2</sup> Werzberg,<sup>3</sup> Gross,<sup>4</sup> and very recently, Sladden.<sup>5</sup> It becomes increasingly evident, as one peruses the literature on pancreatic diagnosis, that there is little uniformity of opinion as to the value of the tests suggested, and general dissatisfaction expressed with practically each of them, most authors suggesting that more than one of these tests be per-

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\* I take pleasure in acknowledging valuable suggestions and assistance on the part of Dr. S. Bookman. I am indebted for autopsy material and microscopic studies to Dr. F. S. Mandlebaum and Dr. William Thalheimer, and to the attending physicians and surgeons of the hospital for the privilege of studying the clinical material.

1. Frank: Arch. f. Verdauungskr., 1912, xviii, 121.

2. Albu: Samml. Zwangloser Abhand. a. d. Gebiet. d. Verdauungskr. u. Stoffwechselskr., 1911, iii, 1.

3. Werzberg: Arch. f. Verdauungskr., 1911, xvii, 533.

4. Gross: Ergebn. d. wissenschaft. Med., 1911, ii, 403.

5. Sladden: Quart. Jour. Med., 1914, vii, 455.

formed and an opinion formed from a general average of the results obtained.

It is difficult, for one not familiar with its intricacies, to appreciate how puzzling and complicated the problem is. Well authenticated cases are on record of the preservation of good health and nutrition with almost complete absence of the gland. On the other hand, severe nutritional disturbance and emaciation may be present in a gland with intact duct system and only a mild chronic inflammatory process taking place. Glycosuria as a symptom of pancreatic disease usually occurs late and with advanced destruction; yet it may be present with what is to-day considered a gland free of organic disease. The question of disturbances of metabolism and food absorption is a more puzzling one, there being even to this day no uniformity of opinion as to whether the external secretion of the pancreas is a prerequisite to normal food absorption and digestion.

The rapidly increasing knowledge of the importance of this organ both to the surgeon and the physician, and the realization of its frequent participation in diseases affecting the upper abdomen, have created a distinct demand for some reliable test that will give an indication of what is taking place in this inaccessible and deeply placed region.

Within the last four years several tubes or catheters have been devised for reaching the duodenum; these have afforded a means of aspirating the contents of this uppermost segment of the small intestine. As this novel means was quite evidently the most rational method of collecting for analysis the external secretion of the pancreas, it has been rather generally adopted. My own studies were begun four years ago, with the aim of demonstrating the presence of ferments in the duodenum, and of using the quantitative analysis of the strength of these enzymes as an index of the functional activity of the gland. In a preliminary paper<sup>6</sup> the question of technic was fully considered and the results of the first twenty-seven cases reported. From such a small series of cases definite conclusions were not possible, but sufficient encouragement was found in the analyses made, to offer the probability of a permanently reliable method. Since that time a larger series of over 120 patients has been studied; this series includes several varieties of pancreatic disease; in these cases additional chemical tests in intestinal absorption have been performed. Necropsies have been performed in a number of them, and in these the valuable opportunity was offered for comparing the existence and strength of the external secretion and the absorptive ability of the intestine for fat and

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6. Crohn: *Proc. Eighth Internat. Congress Applied Chem.*, 1912; *Am. Jour. Med. Sc.*, 1913, cxlv, 393.

nitrogen; in addition the organic condition of the gland was definitely established.

This larger series of cases has afforded another and most valuable fact: one, indeed, quite indispensable to the method, namely, the existence of a normal standard of ferment strength for the external secretion of the pancreas. In the present series of 120 cases, only seventeen showed a deviation from the normal; of these we should exclude six instances in which complete absence of ferments existed, due to tumor obstruction of the ducts. In the remaining 103 cases, a uniform, or as Bondi<sup>7</sup> has called it, "a monotonously uniform" strength of ferments was found. We must accept the figures of these 103 cases as representing the activity of a normal pancreas. In reading the results of the chemical analysis, it is well to compare the activity of each ferment with the average strength of that enzyme as ascertained for normal cases. A general idea will then be had of the activity of the fluid obtained. This is superior to testing for only one ferment. Of the three enzymes calculated, lipase is undoubtedly the most variable, trypsin the most constant. By far the most reliable single index is the tryptic activity, as this protease is found uniformly when the ducts are patent. Normally, 10 c.c. of 0.1 per cent. casein solution is digested in twenty-four hours by duodenal contents in dilution of 1:3,000 to 1:10,000 or even higher dilutions.

The amount of duodenal contents collected cannot be utilized as an index of the amount of pancreatic juice secreted; some cases yield 4 to 5 c.c., some up to 15 to 20 c.c., during the five minutes of moderate continuous aspiration practiced. The strength of the ferments does not vary with the amount aspirated, the enzyme strength of over 90 per cent. of the cases being a constant one in spite of considerable variations in the amount of fluid obtained.

Before proceeding to discuss in detail the results obtained by me in duodenal content examinations, it would be advisable to review the results of similar investigators in the same field, as also the articles which have appeared since the preliminary publication of my first paper.

Einhorn,<sup>8</sup> in 1910, examined the duodenal contents in sixteen cases of various gastric disorders; seven of these cases were instances of achylia gastrica; ferments were present in practically all of these trials, trypsin twice being reported as absent. He further noted the absence of bile in a case of chronic icterus (exact diagnosis not stated).

7. Bondi: Arch. f. Verdauungskr., 1913, xix, 692.

8. Einhorn: Deutsch. med. Wchnschr., 1910, xxxvi, 1519; Jour. Am. Med. Assn., 1910, lv, 6.

Junghans<sup>9</sup> reported results with the Einhorn duodenal bucket (not catheter). In his examinations of fifty cases he succeeded in obtaining duodenal juice in 60 per cent. of his efforts; in a single instance only, one of pancreatitis with fatty stools, the ferments were absent. v. Barth Wehrenalp<sup>10</sup> was less successful with the duodenal bucket, allowing only three hours for the passage of the bucket through the pylorus and into the duodenum. Junghans left the bucket in over night. Their results, however, practically coincide.

Quantitative estimations of the pancreatic ferments were impossible on account of the small amount of fluid obtained with the string and bucket method.

Einhorn and Rosenbloom,<sup>11</sup> using for the first time the duodenal catheter and pump, found fairly constant strengths for the pancreatic ferments obtained; they were further able to demonstrate variations in the outflow of the pancreas, following injections of secretin, hydrochloric acid, sodium bicarbonate, broths, etc.

Crohn<sup>6</sup> reported on twenty-nine cases of various pathological diseases, and a study of a normal control. Constant figures for normal individuals and for persons not suffering from disease of the pancreas were obtained. A case of pancreatitis showed marked diminution of the ferments. Hypertrophic cirrhosis of the liver showed overactivity of the enzymes; in cases of diabetes mellitus the ferments were all present, amylase if anything, being exceedingly active.

Hess,<sup>12</sup> employing an ordinary soft rubber Nélaton catheter in children, demonstrated the presence of amylase, lipase and trypsin in the duodenal contents of new-born and older infants. Little difficulty was experienced in catheterizing the duodenum in a large series of cases. Hess asserts that in two cases of marasmus, paralytic hypersecretion was found; in seven cases of pylorospasm a true functional pancreatic hypersecretion was noted.

In a later paper, Hess<sup>13</sup> reported duodenal catheterization on infants suffering from acute diseases. He again found all the ferments constantly present; trypsin was noted as the most reliable ferment. In thirteen cases of acute intestinal intoxication the ferments were normally present except lipase, which was definitely diminished. Hess suggests that this may account for the poor tolerance of fats in these conditions.

9. Junghans: *Zentralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs.*, 1911, vi, 49.

10. Von Barth Wehrenalp: *Internat. Beitr. z. Path. u. Therap. d. Ernährungsstor. ung.*, 1910, i, 530.

11. Einhorn and Rosenbloom: *THE ARCHIVES INT. MED.*, 1910, vi, 666.

12. Hess: *Am. Jour. Dis. Child.*, 1912, iv, 205.

13. Hess: *Am. Jour. Dis. Child.*, 1913, v, 268.

Ewald, Magnus Levy and Lazarus spoke favorably of the method, though having no personal experience with it.

Oscar Gross<sup>4</sup> denounced the method as impracticable and dangerous, as did also Kleinberger.<sup>14</sup>

Frank<sup>5</sup> reported that he succeeded in recovering duodenal contents in 14 out of 24 cases (60 per cent.). Ferment findings were constant, though no exact quantitative estimations were attempted. In no case was blood ever aspirated. Frank asserts that where duodenal contents are obtained, one has absolutely the best criterion of the functional activity of the pancreas, particularly where quantitatively tested.

G. A. Friedman<sup>15</sup> obtained duodenal contents in all of eighteen cases; marked variations in the quantitative strengths of the ferments prevented him from drawing deductions.

In the last year four interesting reports have been published.

Chace and Myers<sup>16</sup> report on duodenal content examinations in thirty cases. No difficulty was encountered in obtaining the secretion in any of their cases. Active ferments were obtained in all instances, though considerable variation in the strength of these ferments was noted. In a case of hypertrophic liver cirrhosis the ferments were normal, as also in a case of pernicious anemia. In a case of chronic pancreatitis, enzymes, except for a trace of lipase, were absent from the duodenal contents. The variations in gastric acidity in no way influenced the strength of pancreatic enzymes.

Bondi and Solomon<sup>17</sup> never failed to obtain bile and pancreatic ferments in over 100 cases. The strength of the ferments was fairly uniform. In two clinically definite cases of chronic pancreatitis the ferments were absent. These are the only variations from the normal.

Bondi,<sup>7</sup> in a large series of cases, obtained duodenal contents in a fasting state, using water as a test meal. Large variations in the quantity of duodenal contents were found; the ferment strengths, however, are uniformly constant, variations in the three ferments being parallel.

In three cases of cholelithiasis the ferments were diminished. In a case of diabetes the ferments were diminished. Blood was occasionally found, but no significance is laid on this point.

In a recent paper by Einhorn,<sup>18</sup> twenty-four cases were studied. Of six cases of pancreatic lesions, four showed absence of one or two ferments; in two cases of pancreatic tumor, the ferments were present. Cloudy, turbid bile indicates gall-bladder or duct disease, in his opinion.

14. Kleinberger: *Berl. klin. Wehnschr.*, 1909, xlv, 2329.

15. Friedman, G. A.: *Med. Rec.*, New York, 1912, lxxxi, 355.

16. Chace and Myers: *THE ARCHIVES INT. MED.*, 1913, xii, 168.

17. Bondi and Solomon: *Wien. med. Wehnschr.*, 1913, lxiii, 1722.

18. Einhorn: *Am. Jour. Med. Sc.*, 1914, cxlviii, 490.

In general, one may say from the literature, that the Finhorn duodenal tube is the instrument of choice in duodenal instrumentation. With increasing experience, better results, including quantitative estimations, are noted. Fairly uniform figures for ferment strengths are obtained by all the authors. Pancreatic disease is the only one in which serious deviations from the normal occur.

#### REPORTS OF CASES

In my present series, consisting of over 120 cases, 103 cases are regarded as presenting normal pancreatic function; these include many pathological conditions; gastric lesions, benign and malignant, achylia gastrica, organic syphilis, exophthalmic goiter, secondary and primary anemias, malignant growths of various organs, diabetes mellitus, etc. As there is general uniformity of the ferment strengths in all these conditions, it is unnecessary to tabulate each of them separately.

Of the remaining seventeen cases, six presented complete absence of ferments in the duodenum; these are all cases of neoplastic obstruction of the ducts. The eleven other cases represent the instances of diminished pancreatic ferments, due to organic or functional pancreatic disturbance. By comparing the chemical findings of the duodenum with the clinical, operative and, where possible, necropsy data, we will be in a position to ascertain to what extent the results of analysis of duodenal ferments correspond to disease of the pancreas.

The cases may more favorably be divided into groups and separately discussed (Table 1).

#### GROUP A—CASES OF DIMINUTION OF FERMENTS ACCOMPANYING ORGANIC PANCREATIC DISEASE

##### *Cases 1 to 6, inclusive.*

CASE 1.—Acute suppurative pancreatitis, abscess of body and tail of pancreas. Note the marked diminution of ferments, trypsin and amylase being entirely absent.

CASES 2 AND 3.—These are both examples of combined chronic interlobular and intralobular pancreatitis. Both cases show markedly diminished ferments. Both cases at autopsy presented diffuse chronic inflammation of the gland, the cirrhotic tissue infiltrating about and also within the acini. In Case 3, there was, in addition, a small infiltrating carcinoma beginning about the bile duct, but not occluding the pancreatic passages.

CASE 4.—This is one of primary chronic pancreatitis, characterized by jaundice and abdominal pain. At operation, the head of the gland was markedly swollen; no stones were found. The duodenal ferments were only moderately diminished. The patient recovered after cholecystenterostomy.

CASES 5 AND 6.—These are two illustrations of pancreatitis occurring as a complication of gall-stones. Both cases at operation presented cholelithiasis and an enlarged swollen head of the pancreas. Duodenal ferments, in both instances, were definitely diminished.



TABLE 4.—ANALYSIS OF DUODENAL CONTENTS AND DISEASE OF THE PANCREAS

Case	Diagnosis	Duodenal Contents				Absorption Tests				Stool	
		Jaundice	Bile	Fer- ments	Amyl- ase, C.c.	Trypsin, I. : C.c.	Lipase, C.c.	Intake	Output (Stool)	Neutral Fat Globules	Undi- gested Muscle Fiber
1 A B	Acute pancreatitis; ab- scess of tail and body	Slight	+	Very weak	0	0	18	101	....	Absent	Absent
2 S R	Chronic pancreatitis; in- terlobular type	Marked	0	Weak	0	6,000	0	71.3	22 18	Present	Present
3 L V	Chronic pancreatitis; in- terlobular type	Marked	0	Weak	6	700	0	....	....	Absent	Absent
4 M W	Chronic pancreatitis	Moderate	+	Weak	0	3,000	27	....	....	Absent	Absent
5 R M	Subacute pancreatitis; choledithiasis	Absent	+	Weak	0	3,000	0	....	....	Absent	Absent
6 H D	Chronic pancreatitis; cho- ledithiasis	Moderate	+	Weak	3	1,000	0	....	....	Absent	Absent
7 R K	Hepatic cirrhosis; abdom- inal adenitis	Moderate	+	Weak	0	5,000	0	118	18	Absent	Absent
8 A B	Gastric carcinoma; ad- vanced stage	Absent	+	Weak	9	0	18	....	....	Absent	Absent
9 B S	Carcinoma of bile duct and liver	Marked	0	Weak	7	2,000	14	....	....	Absent	Absent
10 H R	Melanotic sarcomatosis	Absent	+	Weak	0	3,000	2.5	....	....	Absent	Absent
11 M F	Adenitis disease	Absent	+	Very weak	0	40	0.6	71.3	....	Absent	Absent
12 L J	Carcinoma of papilla of Vater*	Marked	0	Normal	24.0	30,000	3.3	....	....	Absent	Absent
13 D S	Carcinoma of papilla of Vater*	Marked	0	Normal	12.0	4,300	1.2	....	....	Absent	Absent
14 A B	Chronic pancreatitis; cho- lithiasis	Absent	+	Normal	4.0	10,000	2.1	240	30	Absent	Absent
15 T L	Tumor of head of pancreas	Slight	+	Normal	24.0	20,000	1.5	....	....	Absent	Absent
16 M D	Carcinoma pancreas; ob- structed ducts	Intense	0	Absent	0	0	0	124	20.1	Absent	Absent
17 L K	Carcinoma pancreas; ob- structed ducts	Intense	0	Absent	0	0	0	80.9	11.8	Present	Present

\* Intercurrent obstruction of pancreatic duct; mild interlobular pancreatitis.

GROUP B—CASES OF DIMINISHED FERMENTS WITHOUT ORGANIC CHANGES  
IN THE PANCREAS*Cases 7 to 11, inclusive*

CASE 7 is one of cirrhosis of the liver with moderate jaundice, frequent stools and fever. Pancreatic disease was indicated by diminished ferments in the duodenal contents and poor intestinal absorption, as shown by metabolism studies. At the autopsy several days later, besides the cirrhosis of the liver, large swollen lymph-nodes were found clustered about the head of the pancreas; the pancreas itself was normal grossly and microscopically.

It seems here that some obscure subacute inflammatory process, characterized by lymphadenitis, had taken place in the upper abdomen, centered about the head of this gland. There was a loss in the stool of over 50 per cent of the fat ingested; mechanical obstruction to the duct did not exist. In this case it must be presumed that the pancreas suffered from the disease going on about it; a functional disturbance is noted.

CASES 8, 9 and 10 are examples of tumors in the epigastric region not involving the pancreas, yet having an indirect effect on it by their presence, disturbing the functional activity of the pancreas. In twelve other cases of neoplasms situated variously in the body, this indirect disturbance of the pancreas was absent.

CASE 11 is one of Addison's disease; the diminution in ferments is extreme, this being again an instance of disturbed function from severe disease elsewhere in the body.

## GROUP C—CASES OF NORMAL FERMENTS WITH DISEASE OF THE PANCREAS

*Cases 12 to 15, inclusive.*

CASES 12 and 13 are instances of carcinomata of the papilla of Vater which had caused temporary intermittent obstruction to the ducts and mild secondary pancreatitis. At the time of the examination, ulceration of the tumor into the lumen of the intestine had allowed the escape of pancreatic secretion. The ferments were found in normal concentration in spite of the fact that moderate interlobular inflammation had occurred. The tumor itself, though infiltrating slightly the head of the gland, caused no disturbance in its secretion; neither did the slight chronic inflammation give signs of decreased efficiency. These two cases contrast strongly with Cases 2 and 3, in which chronic inflammation of intra-acinar type caused real damage to the secreting parenchyma.

CASE 14 was one of cholelithiasis and subacute pancreatitis; though the head of the organ was swollen, the elaboration of ferments was in no way interfered with.

CASE 15 was one of tumor of the head of the pancreas not causing obstruction of the ducts. In spite of its presence, the ferments were quite normal.

GROUP D—CASES OF PANCREATIC NEOPLASMS WITH OBSTRUCTION OF THE DUCTS —  
FERMENTS ABSENT*Cases 16 and 17*

There are cases of tumor obstruction of the duct of Wirsung with complete absence of the ferments in the duodenum.

## DEDUCTIONS

The following deductions may be drawn from these cases:

1. Most cases of pancreatitis present deficient external pancreatic secretion.

2. Severe disease in a neighboring abdominal organ may cause diminution of the functional activity of the pancreas.

3. Mild interlobular pancreatitis may exist without diminishing the strength of the external secretion. This is in contrast with intra-acinar inflammation, which causes severe depression of functional activity.

4. Pancreatic new growths, which do not obstruct the duct, do not necessarily cause diminished secretory power.

The first conclusion, that diminished ferments accompany most instances of organic disease, is a logical one and is fully substantiated by the six instances quoted. Some confirmation can be found in the literature. Thus Junghans<sup>9</sup> found in a case of pancreatitis with fatty stools, absence of the ferments in the duodenum. Bondi and Solomon,<sup>17</sup> in two cases of pancreatitis, found identical results. Einhorn,<sup>18</sup> in six cases of pancreatic lesions, noted constant diminution of one or more ferments in the duodenal contents. Similar findings have frequently been noted in the ferment analysis of stools, by Orłowski,<sup>19</sup> Gross,<sup>4</sup> Lifschütz<sup>20</sup> and others. Matko<sup>21</sup> even goes so far as to describe functional hyperchylia, hypochylia and complete achylia pancreatica, on the basis of variations in the tryptic content of the stools.

Unfortunately, the stool analyses for ferments are entirely unreliable; this has been demonstrated by Pratt,<sup>22</sup> who, in four normal individuals, was unable to demonstrate trypsin; also by Tileston,<sup>23</sup> who seven different times examined in vain the feces of a normal individual, not being able to find a trace of trypsin. My own results previously published<sup>6</sup> also demonstrate the unreliability of stool ferment tests as an index of pancreatic functional activity. I there mentioned several instances of normal ferments in the duodenum, but with no trace of enzymes to be noted in the stool. This conclusively proves that, with an open duct and normal pancreatic secretion, the stools may still fail to show ferments.

The examination of ferments in the duodenal contents remains as the one reliable means of ascertaining the strength of the pancreatic ferments.

The second conclusion, that diminished enzymes in the pancreatic secretion may occur with severe disease elsewhere than in the pancreas, is a novel, yet not an unnatural one. For gastric acidity and the gastric ferments similarly vary with severe disease elsewhere in the body, as in pernicious anemia or carcinomatosis. Addison's disease, melanotic

19. Orłowski: *Ztschr. klin. Med.*, 1912, lxxvi, 460.

20. Lifschütz: *Arch. f. Verdauungskr.*, 1913, xix, 562.

21. Matko: *Arch. f. Verdauungskr.*, 1913, xix, 663.

22. Pratt: *Am. Jour. Med. Sc.*, 1912, cxliii, 314.

23. Tileston: *Trans. Assn. Am. Phys.*, 1911, xxvi, 513; *THE ARCHIVES INT. MED.*, 1912, ix, 525.

sarcoma and general carcinoma are examples, in my series, of functional depression of pancreatic enzymes. Sladden,<sup>5</sup> in his excellent critical review of the diagnosis of pancreatic lesions, calls attention to the interdependence of the pancreas on other surrounding organs and observes that it is frequently affected by their diseases. Frank<sup>1</sup> noted a case of peritoneal tuberculosis in which a similar diminution of duodenal enzymes took place. It should not be gathered from these remarks, however, that this consecutive depression of ferments takes place often enough to be an important factor. It is an extremely unusual occurrence. In eighteen cases of abdominal carcinoma it was noted only three times (16 per cent.); it was seen altogether five times in over 120 cases of various diseases.

We may really say that diminution of ferments speaks strongly in favor of pancreatic disease; rarely the presence of severe disease elsewhere in the body may cause a similar finding. This latter fact is at present of more scientific interest than practical value, as it has not yet occurred where the diagnosis of a pancreatic lesion was at issue, but always as an accidental finding while studying large groups of diseases for possible points of interest.

The third conclusion, that pancreatitis, particularly of the chronic interlobular form, may exist without any change in the ferments, is merely corroboration of the fact that not every disturbance of this organ affects its external secretion, or is sufficiently advanced or destructive to cause damage. Clinical experience teaches that a small remnant of functioning gland may preserve metabolism as normally as the whole gland. A similar process of reasoning will explain the existence of normal ferments in the presence of moderately advanced disease, as in case of localized tumor at the head of the pancreas without diminution of the ferments. In this case the duct system was patent. Einhorn<sup>18</sup> had two similar instances in his series.

By comparing the enzyme activity of the external secretion in each case with the necropsy findings, a certain relation is noted between the amount of pancreatic tissue destroyed and the diminution of ferments in the duodenal contents. In Case 1, one of diffuse suppurative pancreatitis with destruction of about five-sixths of the gland tissue, only the faintest trace of ferment remains. In the two cases of chronic intra-acinar pancreatitis, the ferments were moderately diminished; microscopically, a diffuse intra-acinar and interacinar cirrhosis was seen, but a large amount of parenchyma was intact.

In the two cases of temporary obstruction of the excretory ducts by localized neoplasms with secondary pancreatitis of the inter-acinar type, the cirrhosis was slight; the ferments were normal. In these cases the connective tissue surrounded the lobules in larger areas.

sparing the inner secretory portion of the acini. In all four instances there were ample secretory cells intact, showing the definite zymogenic granulation of actively secreting cells.

There is therefore in general, a proportion between the anatomical condition and amount of surviving parenchyma on the one hand, and the enzyme activity of the external secretion on the other. The depression of ferments in cases of primary intralobular pancreatitis is distinctly greater than in those of interlobular inflammation secondary to duct obstruction or inflammation. From this it would seem probable that intralobular pancreatitis is a primary degeneration of the secreting cells, and that the connective tissue increase is only a replacement fibrosis. Interlobular pancreatitis is a connective tissue proliferation, dependent on excretory duct obstruction, inflammation, or vascular changes. The loss of secreting acini and cells is here the sequel of the duct disease.

#### SUMMARY

From the analysis of the external pancreatic secretion obtained by duodenal aspiration, we may say that:

1. Pancreatitis, particularly of the acute inflammatory, or of the chronic intra-acinar type, evidences itself by diminished ferments.
2. Severe abdominal disease may cause a functional hyposecretion of the pancreas.
3. Some cases of pancreatic disease, not associated with widespread destruction of the parenchyma, continue to furnish a secretion of normal enzyme activity.
4. A general gross proportion exists between the amount of surviving parenchyma and the ferment strength of the duodenal contents.

#### *PART II—OBSERVATIONS ON FAT AND NITROGEN METABOLISM IN DISEASES OF THE PANCREAS*

Intimately associated with the question of the entry into the duodenum of the external secretion of the pancreas and the variations in enzyme strength in health and disease, is the subject of the influence of the pancreatic juice on the general metabolism, or in a more restricted sense, on the fat and nitrogen absorption from the intestine. For both animal metabolism studies and absorption observations in human pancreatic disease have failed to present satisfactory or acceptable conclusions on the simple issue, "Is the external secretion of the pancreas essential to good intestinal absorption?"

The failure to solve this problem seems to have rested on the inability to demonstrate conclusively in every instance, experimental and human, that the pancreatic secretion was entirely cut off from the intestine when the observer claimed it to be. Where good absorption

was retained after tying off ducts, the critic drew the inference that some accessory duct had been overlooked. Where the same occurrence took place in a clinical case, the diagnosis of the disease was questioned, or doubt was expressed that the pancreatic duct or ducts were entirely closed by the pathological process at the time of the metabolism study, the necropsy being held several weeks or months later.

The demonstration of the non-patency of the duct at the time of the experiment, has usually rested on the absence of trypsin in the feces, but as has been previously stated, this evidence is untrustworthy.

In the duodenal tube one has an undoubted method of obtaining the contents of the duodenum and of definitely determining both the state of patency of the ducts and the activity of the pancreatic outflow. With these data at hand, absorption experiments could simultaneously be carried on. If, in addition, the organic condition of the gland was ascertainable, we would be in possession of all the data necessary to demonstrate the effect of exclusion of or variations in, the external secretion of the gland on fat and nitrogen metabolism. This fortunate combination of data I have been able to obtain in several cases of human pancreatic disease; absorption experiments and enzyme studies were prosecuted hand in hand; autopsy and pathological reports are furnished in most instances.

Before recounting in detail my own results, let us review in brief the extensive and conflicting literature on the subject:

#### EXPERIMENTAL ANIMAL METABOLISM

The earliest experiments of Claude Bernard<sup>24</sup> consisted of injecting irritating substances into the excretory ducts of the dog's pancreas. By them he established the function of the gland in supplying enzymes to assist in the digestion of food substances. As a result of his experiments, several attempts were made to tie the ducts and note the effect on digestion and absorption; no definite results were obtained. Pawlow<sup>25</sup> noted the retention of good absorption even after the ducts were tied, and in the presence of atrophy of the gland. Von Mering and Minkowski<sup>26</sup> and Minkowski<sup>27</sup> alone, conducted a series of interesting experiments establishing the fact that excision of the gland led to diabetes and almost complete loss of the ability to absorb food from the intestine. Abelman<sup>28</sup>, working under Minkowski, showed that, after

24. Bernard, Claude: *Mémoires sur le pancréas*, 1856.

25. Pawlow: Quoted from Oser, in Nothnagel's *Encyclopedia of Practical Medicine*, 1903.

26. Von Mering and Minkowski: *Arch. exper. Path. u. Pharmacol.*, 1899, xxvi, 371.

27. Minkowski: *Arch. exper. u. Pharmacol.*, 1905, liii, 331.

28. Abelman: *Ausnutzung der Nahrungstoffe nach Pankreas-Extirpation*. Dorpat, 1890.



total extirpation of the pancreas, fat absorption was nil, while nitrogen absorption varied from 30 to 80 per cent. After partial extirpation, absorption was much better (fat 31.5 per cent., emulsified fat [milk] up to 80 per cent.). Sandmeyer's<sup>29</sup> results with partial extirpation are similar to those of Abelmänn. Hedon and Ville<sup>30</sup> demonstrated that, with a biliary fistula alone, the loss of lard in the feces was 55 per cent.; after biliary fistula and partial pancreatectomy the loss of fat rose to 90 per cent. Harley<sup>31</sup> extirpated all but about one-tenth of the tail. The loss of fat was 62.1 per cent., of nitrogen 82 per cent. Rosenberg,<sup>32</sup> on the contrary, found no disturbance of absorption when as little as one quarter of the gland was preserved. He succeeded in causing atrophy of the gland by cutting all the ducts, arteries and veins leading to it (except the main pancreaticoduodenal vessels), yet noted little disturbance of metabolism, though the atrophy was advanced. Zunz and Mayer<sup>33</sup> found little disturbance of absorption after tying the ducts, though atrophy resulted. When the atrophic remnant of gland was removed, however, complete loss of the power to absorb was noted.

Lombroso<sup>34</sup> made a complete study of this question with the following results:

1. After simple ligation of the ducts, fat excretion was 14 to 44 per cent.
2. After extirpation of most of the gland and transplantation of a viable fragment under the skin, fat excretion was 22 to 54 per cent.
3. Ligation of ducts, extirpation of atrophied remnant some weeks later, fat excretion 40, 99 and 113 per cent., respectively, in each of three dogs.
4. In a dog with a viable subcutaneous transplant, the transplant was extirpated. Fat excretion rose rapidly to 97.8, 105 and 96.6 per cent.
5. Wherever the surviving graft was well preserved, good absorption existed, though no ferments were entering the intestine. Lombroso suggested the possibility that the maintenance of good absorption, as long as some living pancreas existed somewhere in the body, was due to the vicarious absorption of the enzymes and resecretion of them through the bile into the intestinal tract. Yet he was never able to demonstrate increased ferments in the bile of such dogs, nor active

29. Sandmeyer: *Ztschr. f. Biol.*, 1894, xxxi, 12.

30. Hedon and Ville: *Compte rend. Soc. de biol.*, 1892, p. 308.

31. Harley: *Jour. Path. and Bacteriol.*, 1895, iii, 245.

32. Rosenberg: *Arch. f. d. ges. Physiol. (Pflüger's)*, 1898, lxx, 371.

33. Zunz and Mayer: *Ref. Jahresb. u. d. Fortschr. d. Thierchem. (Maly's)*, 1905, xxxv, 489.

34. Lombroso: *Arch. f. d. ges. Physiol. (Pflüger's)*, 1906, cxii, 531.

ferments in the intestine of dogs with ligated ducts. Nor was he able to improve the absorption of food by feeding duodenal juice of healthy animals to a dog with extirpated gland.

This painstaking work, as well as all that had gone before it, was criticized by Hess<sup>35</sup> and his pupil Sinn,<sup>36</sup> who pointed out that the pancreas of the dog contained more than one excretory passage, usually three or four; they said that Lombroso's results were due to his having failed to tie off all the ducts in his animals. In two dogs in which Hess tied the ducts he found excretion of fat, 46 per cent. and 95.3 per cent.

Lombroso<sup>37</sup> therefore repeated his experiments and arrived at substantially the same results. He further found that when a Pawlow permanent fistula was made and all the ferments excluded from the intestine, it made no difference in absorption whether the dog licked the outflow of the fistula or not; he concluded that intestinal absorption is independent of the external secretion, but is controlled by a ferment poured internally into the blood.

Burkhardt<sup>38</sup> duplicated Lombroso's experiments and came to diametrically opposite conclusions. When the dog licked the outflow of the fistula, absorption improved; when it was allowed to go to waste, absorption suffered.

Fleckseder<sup>39</sup> repeated these experiments with results similar to those of Lombroso, as did also Niemann.<sup>40</sup> In one of the dogs in which Niemann tied the duct and yet noted good absorption, he examined the duodenum for ferments, at death, but found none, proving that the duct was closed.

Jansen<sup>41</sup> demonstrated fair absorption of fats when an external pancreatic fistula existed; on removal of the graft piece by piece, the loss of fat increased rapidly up to 73.3 per cent.

Brugsch<sup>42</sup> in careful studies denied that absorption was dependent on the external secretion of the gland. He found but slight disturbance on tying the ducts, yet he also could demonstrate no ferments in the duodenum. He presumed the presence of an internal secretion or hormone which regulated absorption; he further attributed part of the loss to delayed motility in the intestine.

Still later work, however, again brings into doubt the conclusions of these various authors.

35. Hess: Arch. f. d. ges. Physiol. (Pfluger's), 1907, cxviii, 536.

36. Sinn: Dissert. Marburg, 1907, p. 29.

37. Lombroso: Arch. f. exper. Path. u. Therap., 1908-9, ix, 99.

38. Burkhardt: Arch. f. exper. Path. u. Pharmacol., 1908, lviii, 251.

39. Fleckseder: Arch. f. exper. u. Pharmacol., 1909, lix, 407.

40. Niemann: Ztschr. f. exper. Path. u. Therap., 1909, v, 466.

41. Jansen: Ztschr. f. physiol. Chem., 1911, lxxii, 158.

42. Brugsch: Ztschr. f. exper. Path. u. Therap., 1909, vi, 326.

Pratt, Lamson and Marks<sup>43</sup> seemed definitely to find in five dogs, deficient absorption of fat and nitrogen on ligation of all the ducts and insertion of omentum between the cut ends, nitrogen loss rising to 77.8 per cent., and fat loss to 88.7 to 95.2 per cent.

Benedict and Pratt,<sup>44</sup> feeding only meat to dogs with tied ducts, found nitrogen losses of 32.1 to 57.7 per cent.

It is most difficult to harmonize the various findings of these many investigators. One explanation alone will satisfy all the requirements: immediately on tying the ducts in animals, atrophy of the gland takes place. If all of the ducts are not ligated the atrophy does not occur. After ligation of the ducts, the resulting disturbance of absorption is dependent on the extent of atrophy resulting. When the atrophy is slight, the absorption remains good; when the gland deterioration is rapid, intestinal absorption is seriously altered. The experiments of Brugsch, Lombroso, Fleckseder and others are difficult to deny, and point definitely to the control of the absorptive processes by a hormone or internal secretion of the pancreas, and to a lesser degree to the direct action of the external secretion. Compensatory overactivity of gastric enzymes, intestinal erepsin, biliary lipase, etc., cannot explain the retention of good absorption with artificially obstructed ducts. Nor is the question answered by suggesting that the ferments are absorbed into the blood from the stagnant contents of the obstructed ducts, and reexcreted through the intestinal wall, for no increase or even maintenance of the usual ferments in the lumen of the intestine has ever been demonstrated.

#### OBSERVATIONS ON ABSORPTION EXPERIMENTS IN HUMAN PANCREATIC DISEASE

Even less conclusive are the results of absorption experiments in persons suffering from disease of this gland.<sup>45</sup>

Disturbances of fat metabolism in diseases of the pancreas were first observed by Kuntzman,<sup>46</sup> and independently by Richard Bright.<sup>47</sup> The latter's own words best describe the symptom of "fatty stool."

43. Pratt, Lamson and Marks: *Tr. Assn. Am. Phys.*, 1909, xxiv, 266.

44. Benedict and Pratt: *Jour. Biol. Chem.*, 1913, xv, 1.

45. In studying fat and nitrogen metabolism in pancreatic disease, it is essential to restrict oneself to cases in which the intake of food was carefully analyzed, as well as the output of feces. Only in this way can conclusions be reached, since analyses merely of stools, or general observations on the character, number, or consistency of the movements, without taking into consideration the nutritive value of the diet, are fallacious.

46. Kuntzman: *Jour. d. Pract. Heilk.*, 1824, lix, 45.

47. Bright, Richard: *Medico-Chirurg. Trans.*, 1833, xviii, 1.

The condition to which I refer is a peculiar condition of the alvine evacuation, a portion more or less considerable assuming the character of an oily substance resembling fat, which either passes separately from the bowel, or soon divides itself from the general mass and lies on the surface, sometimes forming a thick crust, particularly about the edges of the vessel [steatorrhea].

The inconstancy of the symptom and the impossibility of harmonizing it with the pathological conditions were immediately recognized by Bright. For the symptom was present in three cases of carcinoma of the duodenum and head of the pancreas, but was absent in a case of cancer of the pancreas and duodenum in which the ducts were obstructed; also absent in two cases of cancer actually invading the gland, in one of which cases the duct was blocked at the head and enormously dilated.

Some years later Fles<sup>48</sup> made his remarkable observation on the large amount of muscle fibers remaining in the feces in patients suffering from pancreatic disease and Harley<sup>31</sup> and Le Nobel,<sup>49</sup> and Abelmänn<sup>28</sup> noted in animals the increase in nitrogen excretion in similar diseases (azotorrhea).

Clinical observations in the next decades were numerous, but threw no further light on the interesting symptoms. Stimulated by the careful animal experiments of von Mering and Minkowski, accurate chemical observations were begun in 1895; since then the reports of carefully analyzed cases, while numerous, yet do not number more than forty examples.

To avoid monotonous repetition, the cases in the literature are classified and presented in Tables 2, 3 and 4:

TABLE 2.—FAT AND NITROGEN EXCRETION WITH CLOSED PANCREATIC DUCT

Author	Fat Excretion,* Per Cent.	Nitrogen Excretion,* Per Cent.
Brugsch <sup>42</sup> .....	70	25.4
Harley <sup>31</sup> (inflammatory stricture) .....	73	40.0
Pratt <sup>12</sup> .....	58.9	50.9
Peripancreatic cyst, Delfino <sup>12</sup> .....	19.7	
Pancreatic abscess, Umber and Brugsch <sup>37</sup>	59.7	

\* Represents per cent. of ingested fat or nitrogen, which was excreted.

48. Fles: *Holland Arch.*, 1864, ii, 187 (quoted from Robson and Cammidge, "The Pancreas, Its Surgery and Pathology," 1907).

49. Le Nobel: *Jahresb. u. d. Fortschr. d. Tierchem.* (Maly's), 1886, p. 449.

72. Delfino: *Deutsche Ztschr. f. Chir.*, 1913, cxxi, 280.

TABLE 3.—FAT AND NITROGEN EXCRETION IN CHRONIC PANCREATITIS

Author	Jaundice Present	Fat Excretion,* Per Cent.	Nitrogen Excretion,* Per Cent.
Weintraud <sup>73</sup> (hepatic cirrhosis?)..	0	18	46
Weintraud <sup>73</sup> (atrophy of pancreas)	0	22	45
Salomon <sup>70</sup> .....	+	51	69
Glaessner and Sigel <sup>61</sup> .....	0	56.1	41.5
Brugsch and Koenig <sup>74</sup> .....	+	59	
Gigon <sup>75</sup> (calculus cirrhosis) .....	0	20.5	43
Hirschfeld <sup>63</sup> (six cases) .....	0	29.4-47.2	30.4
Keuthe <sup>62</sup> (calculi, atrophy) .....	0	9.8	
Ehrmann <sup>72</sup> (after cholecystenterostomy) .....	0	50.1	42.8
Tileston <sup>23</sup> .....	0	72	62
Barbour <sup>76</sup> (calculi) .....	0	.....	44.2
O. Gross <sup>54</sup> .....	0	55.4	50.8
O. Gross (calculi, atrophy) .....	0	26.2	31
Ehrmann and Krüspe <sup>77</sup> (cholecystenterostomy) .....	0	33.3	34

\* Per cent ingested fat or nitrogen.

TABLE 4.—FAT AND NITROGEN EXCRETION WITH TUMORS OF PANCREAS

Author	Obstructive Jaundice	Fat Excretion,* Per Cent.	Nitrogen Excretion,* Per Cent.
Deucher <sup>78</sup> .....	Slight	83	30
Deucher <sup>78</sup> (cholecystenterostomy) ..	0	52.6	19
Brugsch <sup>42</sup> .....	+	85	39
Brugsch <sup>42</sup> .....	+	64	20
E. Meyer <sup>79</sup> (carcinoma of head) ..	+	38	34-41
Adler and Milchner <sup>80</sup> .....	+	18	
Wynhausen <sup>80</sup> .....	.....	73.6	
Brugsch <sup>81</sup> (ducts closed) .....	+	60	32.9
Albu <sup>7</sup> (cancer and atrophy) .....	+	79	36
Tileston <sup>23</sup> .....	+	75.6	19.8
Tileston <sup>23</sup> .....	+	68	
Tileston <sup>23</sup> .....	+	52.6	14.5
Tileston <sup>23</sup> .....	+	45.6	21.1
Tileston <sup>23</sup> .....	+	49.1	
Pratt <sup>22</sup> .....	0	79.9	34.8

\* Per cent. of ingested fat or nitrogen.

73. Weintraud: Die Heilkunde, 1898, iii, 67

74. Brugsch and Konig: Berl. klin. Wchnschr., 1905, xlii, 1605.

75. Gigon: Ztschr. f. klin. Med., 1907, lxxiii, 420.

76. Barbour: THE ARCHIVES INT. MED., 1911, viii, 662.

77. Ehrmann and Krüspe: Ztschr. f. klin. Med., 1913, lxxviii, 122.

78. Deucher: Cor.-Bl. f. schweiz. Aerzte, 1898, xxviii, 321.

79. Meyer, E.: Ztschr. f. exper. Path. u. therap., 1906, iii, 58.

80. Wynhausen: Berl. klin. Wchnschr., 1909, xlii, 1406.

81. Brugsch: Ztschr. f. klin. Med., 1905, lviii, 518.

Before critically analyzing these tabulations, it is essential again to recall that in most of the cases no mention is made of the patency of the pancreatic duct; further, many of the cases were not observed at autopsy, the clinical diagnosis alone determining the nature of the malady. Even autopsy descriptions often fail to detail the condition of the gland, and microscopic studies are very rare.

From these tables, however, we may note the following general averages:

Simple closure of the pancreatic duct, nitrogen loss, 38.8 per cent.; fat loss, 67.3 per cent.; acute pancreatitis abscess, nitrogen loss, 21 per cent.; fat loss, 59.7 per cent.; chronic pancreatitis, nitrogen loss, 46.3 per cent.; fat loss, 39.3 per cent.; tumors of pancreas, nitrogen loss, 28.6 per cent.; fat loss, 62.3 per cent.; pancreatic cyst, fat loss, 19.7 per cent. The figures for the normal excretion of fat and nitrogen, as given by Schmidt and Strassburger<sup>50</sup> are, nitrogen, 4 to 6 per cent.; fat, 12 to 16 per cent. In simple obstructive jaundice, the fat excretion increases to 20 to 30 per cent.; nitrogen absorption is practically unaffected.

Conclusions from these tables of absorption tests in man are most difficult, for all the cases were instances of advanced disease of the gland, sometimes associated with closure of the duct, and always with advanced disorganization of the parenchyma. Early examples of the disease and mild cases do not appear, as the clinical diagnosis in such cases before the appearance of the typical stool changes is never made.

From Table 5 we observe that simple benign cyst of the pancreas causes little disturbance of absorption; acute and chronic pancreatitis give rise to moderately severe disturbance, the nitrogen excretion rising to 21 to 46.3 per cent., and fat excretion to 39.3 to 59.7 per cent. Malignant neoplasms demonstrate a higher fat loss amounting to an average of 62.3 per cent., individual variations ranging from 30 to 83 per cent.

To the tabulated instances in the literature, I am able to add seven examples of careful absorption experiments in diseases of the pancreas. In all of these cases, duodenal contents obtained at the moment of the chemical studies, definitely determined the patency or non-patency of the pancreatic and bile ducts, as also the condition of the pancreatic external secretion. Careful autopsy studies accompany many of the cases.

#### TECHNIC

As an index of pancreatic metabolism, fat and nitrogen absorption tests were chosen. Though Fr. Müller<sup>51</sup> held that the poor absorption of these substances was due to poor digestion and preparation of the food in the intestine, as evidenced by diminished saponification, later observers have not confirmed this contention. Brugsch<sup>42</sup> experimentally

50. Schmidt and Strassburger: *Die Feces des Menschen*, Berlin, 1905.

51. Müller, Fr.: *Ztschr. f. klin. Med.*, 1887, xii, 45.



demonstrated normal protein digestion and amino-acid formation in dogs with ligated ducts, and numerous clinical observers have frequently shown normal fat splitting and saponification in the intestine of human instances of pancreatic diseases (Tileston,<sup>23</sup> Pratt<sup>22</sup> and others). In later years, therefore, most workers have limited themselves to ascertaining absorption of food products; the claim of Bondi and Bondi,<sup>32</sup> that epithelial degeneration took place in the mucosa of the intestinal tract has found no confirmation and few believers. Nor will interference with intestinal and gastric motility account for the symptom of disturbed nutritional equilibrium as suggested by von Noorden<sup>53</sup> and by Brugsch.<sup>42</sup>

The diet employed for absorption experiments consisted of the following: Milk, 1,500 to 2,000 c.c. a day; eggs, three a day; bread, 100 gm. daily; cereal, 100 to 200 gm.; meat, about 50 gm., with fat, daily; water, normal amounts. The diet was varied in amount to suit individual requirements, some patients being unable to eat all that was tendered to them; however, when possible, uniformity in the amount and character of the food was preserved. The diet has a daily equivalent of about 120 gm. of fat, and 15 gm. of nitrogen. Gross<sup>54</sup> has shown that absorption varies very little with the quantity of food given, practically the same percentage of fat and nitrogen being absorbed with large variations in the food intake.

The absorption test was begun by the administration to the patient of a low saline enema, the return of which was discarded. The designated diet was then begun, a complete duplicate diet being sent to the laboratory for analysis. The diet and the collection of specimens of the stool were continued for two days, at the end of which period another enema was given. This enema was added to the collection of feces, the whole being sent to the laboratory. On receipt in the laboratory, macroscopic and microscopic examinations were made on the stool; the food, after the addition of alcohol, was dried to approximately constant weight over the water-bath. The stool was similarly dried; both feces and food were then ground in a mortar and pulverized. When the stool was too oleaginous for grinding it was first frozen, then ground. Nitrogen values were ascertained by means of the Kjeldahl process; fat by the Kumagawa-Suto<sup>55</sup> method.

In most of the cases in this series, one or two intestinal movements a day was the rule; more frequent evacuations were very exceptional. In no case was organic intestinal disease present, nor was intestinal or abdominal tuberculosis a factor. Both these latter conditions have been demonstrated by Fr. Müller<sup>51</sup> to cause disturbed absorption. Jaundice was present in most of my cases, usually a complete obstruction of the bile duct. To establish definitely a figure for absorption in cases of complete biliary obstruction, a preliminary test was carried out on a case of carcinoma of the bile duct with total occlusion of bile, but with

52. Bondi, S., and Bondi, J.: *Ztschr. f. exper. Path. u. Therap.*, 1909, vi, 254.

53. Von Noorden: *Handb. d. Path. d. Stoffwechsel.*, 1906.

54. Gross, O.: *Deutsch. Arch. f. klin. Med.*, 1912, cvii, 106.

55. Kumagawa-Suto: *Biochem. Ztschr.*, 1908, viii, 252.

normal pancreatic function and demonstrated by the duodenal tube. The excretion of fat was 32 per cent.; of nitrogen 6.6 per cent. This may be accepted as a control figure for a case of complete acholia. The difference between this figure and higher figures in the following series, would represent the pancreatic factor.

The results of the absorption tests on my series of pancreatic diseases is as shown in Table 5:

TABLE 5.—ABSORPTION TESTS \*

Case	Diagnosis	Jaundice	Duodenal Contents		Intake		Output	
			Bile	Ferments	Fat	Nitrogen	Fat	Nitrogen
1. A. B.	Acute pancreatitis; abscess	Slight	+	Very weak	101	....	9.5( 9.4%)	
Group 2								
2. S. R.	Chronic pancreatitis, intralobular	Marked	0	Weak	71.3	22.18	24.7(34.7%)	3.6(16.4%)
3. A. B.	Chronic pancreatitis, cholelithiasis	Absent	+	Normal	240.0	30.0	13.8( 5.6%)	1.8( 6 %)
Group 3								
4. R. K.	Hepatic cirrhosis; abdominal adenitis	Moderate	+	Weak	118	18	57.6(51.3%)	3.4(18.7%)
5. M. F.	Addison's disease..	Absent	+	Very weak	71.3	....	18.7(26.2%)	
Group 4								
6. M. D.	Carcinoma of pancreas	Intense	0	Absent	124	20.1	35 (28.2%)	2.2 (11%)
7. L. K.	Carcinoma of pancreas	Intense	0	Absent	80.9	11.8	48.4(60 %)	1.86 (15%)

\* This table is a rearrangement of the cases in Table 1

Group 1. Fat absorption studies in a case of acute suppurative pancreatitis with severe diminution of all the ferments (very slight jaundice) demonstrated that on an intake of 101 gm. of fat, 9.5 gm., or 9.4 per cent., were excreted from the bowel. Of the excreted fat, 42 per cent. was neutral, 58 per cent. was split (fatty acids and soaps).

At the necropsy the body and tail of the gland were found to be entirely destroyed, only the head and a small portion about the duodenum being preserved. The duct of Wirsung was patent.

In this case, in spite of marked destruction of the gland, and extensive diminution of the ferments in the external secretion, the absorption of fat was excellent, thereby demonstrating that a small portion of intact pancreas can maintain absorption equilibrium, *even when the enzymes excreted into the intestine are markedly diminished*. In the stool no evidence of neutral fat was observed.

Group 2 comprises two cases of chronic pancreatitis (Cases 2 and 3, Table 5). Case 2 is one of moderately severe intralobular inflammation, causing, in addition, stricture of the bile duct (duodenal tube and necropsy). At the time of the test the ferments were markedly diminished, and bile was absent. The stools contained a few neutral fat globules and undigested muscle fibers. Absorption experiments demonstrated that on an intake of 71.3 gm. of fat and 22.18 gm. nitrogen, there was a fecal loss of 34.7 per cent. fat, and 16.4 per cent. of the ingested nitrogen.

Case 3 was one of mild pancreatitis with swelling of the head of the gland as shown at the operation. At the time of the metabolism test the duodenal tube demonstrated normal enzymes and normal quantity of bile. On an intake of 240 gm. of fat and 30 gm. nitrogen there was an excretion of 5.6 per cent. fat and 6 per cent. nitrogen; in other words, normal conditions.

Group 3 entails the discussion of two cases of functional depression of the pancreas caused by severe disease elsewhere in the body (Cases 4 and 5, Table 5). Both cases showed diminution in the enzyme activity of the duodenal contents; normal amounts of bile were entering the intestine.

Case 4 was one of cirrhosis of the liver with abdominal lymphadenitis; the parenchyma of the gland was microscopically and macroscopically normal. Absorption tests demonstrated that on an intake of 118 gm. fat and 18 gm. nitrogen there was an excretion of 51.3 per cent. fat and 18.7 per cent. nitrogen.

Case 5 was one of Addison's disease (clinical diagnosis). At the time of the test, duodenal ferments were definitely diminished; bile was abundant. On an intake of 71.3 gm. fat, 26.2 per cent. was excreted.

These two cases demonstrate that functional depression of the pancreas causes definite and marked interference with the absorption of food, and this, too, be it remembered, without evidence of organic disease of the secretory cells.

Group 4 comprises two cases of complete obstruction of the pancreatic duct by neoplasms. Complete biliary occlusion existed in both instances. Case 6 was observed in the first week of illness. On an intake of 124 gm. fat and 20 gm. nitrogen there was an excretion of 28.2 per cent. fat and 11 per cent. nitrogen. The complete acholia would account for the loss of 28 per cent. fat; the slight increase of nitrogen loss to 11 per cent. is the only result of complete absence of

ferments of the pancreas in the intestine.<sup>56</sup> As this patient was examined in the first week of symptoms, it may be presumed that the body of the gland was still intact, as innumerable animal experiments show that the process of atrophy which results on closure of the duct is a gradual one, taking time for its full development. Neutral fat globules and undigested muscle fibers were absent from the stool.

Case 7 (Table 5) differs from the former in that it was seen only after the malignant process had been in existence over three months. The duodenal tube demonstrated, at the time of the absorption experiments, complete closure of the bile and pancreatic ducts. Neutral fat globules and undigested muscle fibers appeared in the stool two weeks after the period of the absorption tests. On an intake of 80.9 gm. fat and 11.8 gm. nitrogen, there was an excretion of 60 per cent. fat and 15 per cent. nitrogen. The large loss of fat and protein was accounted for by the autopsy report; complete infiltration of all the pancreas by invading carcinoma; the portions of the parenchyma not actually destroyed by the new growth were atrophic and replaced by cirrhotic connective tissue.

Three main conclusions may be drawn from these absorption tests in pancreatic diseases:

1. The nature of the disease does not determine the degree of fat and nitrogen loss.
2. The amount of food absorption is independent of the patency of the duct, or the activity of the enzymes of the external secretion of the gland.
3. The degree of interference with intestinal absorption is dependent on organic disease or functional derangement of the parenchyma of the gland, the pancreas probably normally controlling intestinal absorption by an internal secretion or hormone.

In substantiation of the first conclusion we may point to the wide divergence between the figures for absorption in the several diseases. In acute suppurative pancreatitis, for instance, the fat loss in Case 1 of my series is 9.4 per cent.; in a case reported by Umber and

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56. It might be suggested in this case, that a patent accessory duct of Santorini supplied ferments to the intestine. Careful dissection in six cases of obstruction of the duct of Wirsung failed to show any instance of a patent accessory duct. Nor have any of the observers of pancreatic disease noted a patent accessory duct, except Tileston<sup>23</sup> who once found it. However, the duodenal tube, lying deep in the intestine, would not differentiate between main and accessory ducts; if ferments are being secreted it would discover them. When no ferments are found, it is safe to assume that all ducts are closed, as the Santorini duct in man opens with, or within a centimeter or two of the Vaterian papilla. At autopsy the accessory duct has often been seen, but never patent through to the lumen of the intestine.

Brugsch<sup>57</sup> (Table 2), this same loss was 59.7 per cent., or five times as great. In Cases 2 and 3 of my series the fat loss varied from 5.6 per cent. to 34.7 per cent., and the nitrogen loss from 6 per cent. to 16.4 per cent. A glance at Table 3 of the literature will demonstrate still greater variations.

In two cases of obstructing pancreatic tumors in my series, Case 6 shows the moderate losses of 28 per cent. fat and 11 per cent. nitrogen, while Case 7 presents a loss of 60 per cent. fat (more than double) and 15 per cent. nitrogen. A glance at Table 4 of the literature brings to light still greater divergences.

It is then evident that the nature of the disease plays a small rôle in determining the degree of food loss.

In substantiation of the second deduction, that the external secretion of the pancreas influences food absorption in only a small way, we note that absorption is equally good in Case 1 with almost completely absent ferments, Case 6 with no ferments at all in the intestinal tract, and Case 3 with normally active enzymes being secreted. Absorption is almost identical in all three instances in spite of the great divergence in the condition of the ferments.

Against the deduction that absorption is little disturbed by diseases depressing the enzyme secretion of the pancreas, may be offered the argument that compensatory overactivity of the gastric, salivary, or intestinal ferments (erepsin) may substitute itself for the former diminution (Meltzer, "Factors of Safety," in discussion of Tileston's paper<sup>23</sup>). But if we refer back to the section of this article on Experimental Pancreatic Disease, we will recall that all attempts to demonstrate such compensatory overactivity were futile. Failure also attended efforts to demonstrate absorption of stagnant ferment from obstructed ducts and reexcretion through the intestinal wall into the lumen of the gut. Experimentally, when the ducts are tied, trypsin is absent from the intestine (Brugsch,<sup>42</sup> Werzberg,<sup>3</sup> Lombroso<sup>34</sup>). The same fact holds good for human cases of obstructed ducts (Orlowski,<sup>19</sup> Gross,<sup>4</sup> Pratt,<sup>22</sup> Tileston,<sup>23</sup> Crohn,<sup>6</sup> Matko<sup>21</sup> and others).

After consideration of my own cases and of the experimental work the evidence fails to show that the external secretion of the pancreas is essential to good absorption.

In substantiation of the third deduction, that the degree of interference with absorption depends on organic or functional disturbances of the secretory parenchyma of the gland, we may bring the following evidence:

Of the two cases of pancreatitis in Group 2 (Table 5), in Case 2 the process was severe, general throughout the gland, intralobular in

57. Umber and Brugsch: Arch. f. exper. Path. u. Pharmakol., 1906, lv, 164.

form; every lobule had been attacked, within and without, by connective tissue, as shown by the autopsy. The absorption test showed a loss of 34.7 per cent. fat and 16.4 per cent. nitrogen. In Case 3, with swelling only of the head of the gland, relieved by operation, absorption was quite normal. Of the two cases of neoplastic obstruction of the ducts (Cases 6 and 7), absorption in the one examined early was still very good; in the patient examined late in the course of the disease (complete infiltration and atrophy of acini), absorption had suffered greatly.

Confirmation of this contention from the literature is difficult, as so few detailed necropsy reports exist, and the extent of destruction is so rarely mentioned. Moreover, the literature offers only such cases as demonstrated clinically free neutral fat or undigested muscle fibers in the stools or had the numerous, bulky, oleaginous evacuations typical of pancreatic disease. As this symptom, in my experience and in that of others, is a late one to appear, and indicates advanced disease, we naturally expect to find marked interference with absorption. Exact chemical methods in all these published cases do show severe losses in the food absorption.

If, on the other hand, we attribute the degree of food loss to the nature of the attacking disease, we find no consistent ground for such a classification. Pancreatitis cases vary in their fat losses between 9 per cent. and 72 per cent.; tumor cases vary between 18 per cent. and 85 per cent., or practically identical limits. Nitrogen losses vary similarly. The explanation is not to be sought in the nature of the malady, but in the amount of tissue destruction or functional disarrangement brought about within the gland. Thus, every case must be judged by itself, and the disturbance of gland function estimated by the degree of unabsorbed food.

Could one demonstrate a direct proportion between absorption interference and parenchyma disorganization, the problem would be solved. But the exceptions to such a rule are too numerous. Richard Bright noted this when he made his first observations on fatty stools. Franke<sup>58</sup> published three cases of complete excision of the pancreas for cancer without the development of glycosuria or fatty stools (one case observed for five months). Adler and Milchner<sup>59</sup> observed a case of abdominal tumor, with severe glycosuria and jaundice, yet excreting only 18 per cent. of the ingested fat. Walker<sup>60</sup> reports the case of a man observed for twenty-six years, who at necropsy showed pancreatic calculi blocking the duct and advanced atrophy of the parenchyma.

58. Franke: *Arch. f. klin. Chir.*, 1901, lxiv, 364.

59. Adler and Milchner: *Berl. klin. Wchnschr.*, 1908, xlv, 1487.

60. Walker: *Med. Chir. Tr.*, 1889, lxxii, 257.



yet never developed glycosuria or fatty stools or other evidence of disease of the gland.

The most flagrant exception to the rule is the case reported by Glaessner and Sigel,<sup>61</sup> one of chronic pancreatitis. In this case there was a loss of 56.1 per cent. fat and 41.5 per cent. nitrogen. Five years later, Keuthe<sup>62</sup> performed absorption experiments on this same individual and discovered normal metabolism. At the autopsy (death due to pulmonary tuberculosis) pancreatic calculi and complete atrophy of the gland were found. No accessory pancreas was discovered.

These exceptional instances can be explained on only one common basis, namely, that small remnants of surviving parenchyma *can* and do preserve normal metabolism. But there is another factor besides the amount and size of the surviving fragment, and that is the functional capability of this remnant. This point is amply verified by the experiments of Lombroso, Fleckseder, Niemann and others who demonstrated nutritional equilibrium when a minute transplant of pancreas remained viable under the skin.

But if a small fragment of secreting tissue can maintain good absorption, why do we constantly observe severe disturbances in metabolism when the gland is largely preserved, showing only a moderate degree of chronic intra-acinar inflammation, but with large areas of well preserved and apparently actively secreting zymogenic cells? This query brings the same answer, that *not the amount but the functional activity of the surviving cells* determines the degree of balance or loss of equilibrium. It may be that chronic intra-acinar pancreatitis is, as suggested in an earlier paragraph, a primary degeneration of the secretory cells, not visible with our present microscopic methods, and involving that internal secretion of the gland which controls absorption, and so often carbohydrate metabolism. In that event the connective tissue would be only a replacement fibrosis, of no importance as an index of the severity of the disease.

That functional deterioration of the *external* pancreatic secretion may occur without organic disease was shown by the enzyme studies in Part 1 of this paper (Cases 7-11, Table 1). A similar functional deterioration may affect the *internal* secretion of the gland, resulting in disturbed absorption (Cases 4 and 5, Table 5). The present conception of the mechanism of the production of diabetes mellitus is founded on the idea of a similar disturbance to an internal secretion of the pancreas; here, too, it has frequently been impossible to demonstrate an organic lesion to the gland, even with the finest methods. Organic disease, sufficiently advanced to cause both diabetes and dis-

61. Glaessner and Sigel: Berl. klin. Wehnschr., 1904, xli, 440.

62. Keuthe: Berl. klin. Wehnschr., 1909, xlvi, 47.

turbed metabolism, may exist, though this is rare. Such cases were clearly described by Hirschfeld<sup>63</sup> in 1891. Fortunately, coexistent disturbance of both the internal secretions of the pancreas is unusual; fatty stools in diabetes are exceedingly rare, and glycosuria as a symptom of pancreatitis occurs only in 38 per cent. of cases according to Fitz,<sup>64</sup> and only 5.3 per cent. as given by Deaver.<sup>65</sup> The two internal secretions of the pancreas are separate entities, sometimes, but not usually, being simultaneously involved in disease, and being differently affected by the various pathological processes that affect the gland. We should recognize disturbances of both these internal secretions as due to organic disease, as also to *functional* derangement of the parenchyma.

It is probable also that the disturbance of fat absorption in a case of congenital steatorrhea, reported by Garrod and Hurtley,<sup>66</sup> is explainable on the basis of the congenital absence of such an internal secretion. In the same category can probably be included the case of pancreatic infantilism described by Bramwell.<sup>67</sup> Also the occurrence of fatty stools in some cases of exophthalmic goiter, described by Bittorf,<sup>68</sup> in which a general disturbance of polyglandular secretions may exist. The peculiar disease reported by Whipple,<sup>69</sup> in which large deposits of fat and fatty acids occurred in the intestinal and mesenteric lymphatic tissue, may fall into the same category.

Many workers in the field of pancreatic disease have noted a marked improvement in the absorption of both fat and nitrogen on feeding pancreatic extracts or the raw gland (Salomon,<sup>70</sup> Ehrmann,<sup>71</sup> Gross,<sup>61</sup> etc.). This has been held as a proof that the external secretion of the gland controls digestion and absorption. To controvert this argument there are two strong facts. First, with even excessive feeding of commercial extracts of raw gland, no ferments were demonstrable in the intestine, though the absorption of food had markedly improved. Second, my own analyses of the known market products prove them either inactive or so weak as to be incapable of replacing such strong ferments as the gland normally supplies. Yet the improvement in absorption after feeding the gland is beyond question. The explanation lies in the fact that both commercial and raw extracts prob-

63. Hirschfeld: Ztschr. f. klin. Med., 1891, xix, 294.

64. Fitz: Tr. Congr. Am. Phys. and Surg., 1903, vi, 36.

65. Deaver: Jour. Am. Med. Assn., 1911, lvi, 1079.

66. Garrod and Hurtley: Quart. Jour. Med., 1912, vi, 242.

67. Bramwell: Quoted from Robson and Canmidge, *The Pancreas, Its Surgery and Pathology*, 1907.

68. Bittorf: Deutsch. med. Wchnschr., 1912, xxxviii, 1034.

69. Whipple: Bull. Johns Hopkins Hosp., 1907, xviii, 382.

70. Salomon: Berl. klin. Wchnschr., 1902, xxxix, 45.

71. Ehrmann: Ztschr. f. klin. Med., 1909-10, lxix, 319.

ably contain the internal secretion of the gland in an active form, just as does commercial thyroid or pituitary extract.

We may summarize by saying that cases with distinct increase of fat and nitrogen excretion, not due to intestinal disease or abdominal tuberculosis, and greater than the fat loss due to simple biliary obstruction, are strongly indicative of pancreatic disease. From the absorption test, the diagnosis of the nature of the disease is not vouchsafed, but an impression is gained of the functional activity of the surviving glandular tissue. The absorption test also offers no knowledge of the condition of patency or non-patency of the ducts, nor of the activity of the external secretion.

#### GENERAL CONCLUSIONS

1. The quantitative examination of duodenal ferments is the most rational and accurate method of studying the external secretion of the pancreas. Diminution of such enzyme activity of the pancreas is a reliable sign of organic disease of the gland. Occasionally, though rarely, a diminution of ferments occurs as a symptom of advanced organic disease elsewhere in the body. Roughly, the diminution of ferments is directly proportional to the extent of organic destruction which has taken place.

2. The absorption of fat and nitrogen from the intestine is independent of the condition of the external secretion, or even of its presence. Absorption may be poor with an intact gland, or good with a gland of which only a fragment survives the disease. The functional activity of the gland, not its organic condition, determines the degree of absorption; this is probably controlled by an internal secretion or hormone.

3. Duodenal ferment tests give the index of the organic condition of the gland. Absorption tests give the index of the functional activity of the pancreas.

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# A DIFFERENTIAL STUDY OF COCCIDIOIDAL GRANULOMA AND BLASTOMYCOSIS

## I. PATHOLOGY AND BACTERIOLOGY

## II. REPORT OF TWO ADDITIONAL CASES OF COCCIDIOIDAL DISEASE \*

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To California physicians who have seen a good deal of a disease peculiar to the San Joaquin Valley and described as coccidioidal granuloma there seems to be a confusion on the part of some writers as to its relation to blastomycosis, and indeed, the two have been frequently referred to as one and the same disease. It is our purpose to show how real the confusion is in the literature, and by describing the morphology of the two organisms, their development and appearance in tissue, as well as the reactions found, and finally by a comparison of the effect of each form on inoculated animals, to show that they are distinctly different and not merely different forms of the same organism with different methods of development and different toxicity under varying conditions. This latter view is held by Wright, who in his article on the subject in Osler's "System of Medicine," regards all the cases reported under the names coccidioidal granuloma and blastomycosis as different manifestations of the same disease, which he calls *oidiomycosis*. He states that the prognosis is bad where the condition is due to infection with sporulating forms, whereas only four of thirty patients died when infection was with budding forms. He discusses briefly Wollbach's morphological studies and animal work with the sporulating forms, and considers the budding forms another phase of the same organism.

Whitman, who studied a case of "systemic blastomycosis" in Denver, recognizes the confusion which exists and in an article on the "Botany of the Organism of Blastomycosis," states that "the organisms in these cases are probably not identical." The importance of budding referred to by many authors as a different morphological characteristic is set aside by him as having no biological significance and no longer

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used by mycologists on account of its being found so widely distributed among fungi. "There is apparently ample ground for the view that the term 'blastomycosis' really includes a wide variety of organisms. Cultures from different cases present considerable variations in morphology and cultural characteristics." An abundance of budding forms marked some, whereas an absence characterized others. Some recovered rapidly under potassium iodid, whereas others progressed obstinately in spite of it.

In his case, Whitman says: "I have observed for the first time the production of mycelia within the tissues." He traces the development of asci in the tissues and states that budding forms are exceedingly rare. He concludes that the plant may belong to the *Monascaceae* or *Exoascaceae* in the *ascomycetes* group, and that a study of the behavior of this organism under conditions natural to the life of related groups would possibly give complete information regarding its botanical position.

Brewer's case of an abscess in the back, connected with the lumbar vertebrae, was studied by Wood, who reported the pus showing large numbers of spherical cells of different sizes (from 10 to 25 microns), each surrounded by a clear gelatinous envelope. No budding was found in the organisms as seen in fresh pus and mycelia were not observed in cultures, which grew easily but slowly on ordinary mediums.

Zinsser discussed the morphological characteristics of the organism found in Brewer's case of blastomycosis. Unlike most forms described, his organism grew poorly on all fluid mediums. Reproduction was by budding, and in no case even in agar and gelatin hanging drops were mycelia observed. In old cultures daughter cells grew and budded again without detachment entirely from the mother cell.

Ewing, in the discussion, reported a case in Coley's service from which an organism with abundant mycelia was cultivated. The organism grew at room temperature and even in the ice-box.

Irons and Graham's case of generalized blastomycosis showed no special points of interest except the belief that the primary lesion was in the lungs. Although they state, as is generally believed, that dissemination is by the blood-stream, two blood-cultures were sterile. Cultures on ordinary mediums showed elevated, mold-like, definitely margined growths with aerial hyphae and mycelia. Budding forms were found in young cultures.

Morris of New York reported as systemic blastomycosis the case of a physician from Texas who infected his finger the year before while dissecting in Chicago. MacNeal and Hjelm, who made the cultures and discussed the diagnosis in the same journal, described the organism

as growing after forty-eight hours' incubation in "radiating mycelial threads." The fresh pus contained double contoured spheres (from 4 to 25 microns). No budding forms or mycelial threads were recognized in the pus, but in growths the mycelia were abundant. They regarded the organism as "identical with that discovered by Posada and Wernicke and first described in the United States by Rixford, who bestowed on it the name *Coccidioides immitis*."

Buschke<sup>1</sup> discussed at length the "*Heftähnliche Microorganism*." In the oidiomycotic infections of tissue he states that the oval bodies alone are found, mycelia having been observed by no authors. Gilchrist's disease he calls *Oidiomycosis americana*, and the coccidioidal granuloma cases of Ophüls and Moffitt and other American authors he regards as the same affection. He would group them under the heading of blastomycosis.

A detailed review of the literature on coccidioidal disease and blastomycosis has not been attempted by us. Ricketts presented an exhaustive study, in 1901, of the clinical and laboratory aspects of the disease and concluded that the so-called "protozoic disease" (coccidioides) of Posadas, Wernicke and Ophüls, and Gilchrist's blastomycotic dermatitis were various manifestations of the same disease. He described the lesions of blastomycosis consisting of subcutaneous abscesses or granulomatous nodular growths with usually the appearance of a primary papule. The abscesses had a cauliflower-like surface with elevated borders and surrounded by a red, indurated zone. The centers of the lesions showed granulations. Marked epithelial hyperplasia was noted as well as epidermal and subepidermal abscesses. Dense infiltrations of cells, including giant-cells, were noted. Vast numbers of organisms were found in some cases in the pus and granulation tissue. In the viscera small nodular masses and abscesses with and without cheesy material developed. A comparative study of the organisms, including blastomycetes or oidiomycetes and the organism of Ophüls and Moffitt's "so-called protozoic disease," revealed practically no differences. At least there appeared to be no greater differences than between the various strains of blastomycetes. Most of the organisms developed on artificial mediums in one or two days, certain others requiring from two to seven days. He divided the entire group (including Busse's *Saccharomycosis hominis*, and Curtis' *Saccharomycosis humaine*) into three classes, depending on the appearance of growth on culture mediums: (1) elevated, moist, white colonies coalescing to form a fleshy growth of paste-like consistency; (2) granular surface, slightly elevated and on coalescing, more elevated and

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1. Buschke: In Kollé and Wassermann's Handbuch der path. Mikroorganismen, xv, 155-210.



eventually a surface looking like a piece of crumpled cloth or mass of earthworms; (3) aerial hyphae and surface white, dry and flour-like and eventually covering sides of container. Some of the organisms produced acetic acid; some fermented glucose and maltose, and others fermented saccharose and lactose, while others had no fermentative activity. One produced indol. A complete study of the "protozoic" organism appears not to have been made. Experimental inoculations showed considerable resistance to infection by the various strains of blastomycetes on the part of guinea-pigs, dogs and rabbits.

In 1904 Wolbach studied a strain of coccidioidal organisms isolated from a patient with subcutaneous lesions. Growth appeared in culture mediums in two to seven days, and after some time it showed on solid mediums an opaque white, elevated center due to aerial hyphae bearing gonidia. In broth globular, white, thistle-down-like masses developed and settled to the bottom of the tube. Saccharose, dextrose and mannite were not fermented. Microscopically, the growth showed radiating masses of coarse, branching, segmented mycelia with distinct membrane. In very old cultures spherical bodies were found resembling those found in tissues. The organism was highly virulent for guinea-pigs and rabbits, and the lesions simulated tuberculosis. Endogenous reproduction was found in the organisms recovered from the animals. No evidences of mycelia or budding processes were noted, although the latter were in some instances simulated owing to juxtaposition of the cells. The development of mycelia from the endospore cell as found in pus was studied on agar slides and hanging-drop preparations and the reverse development by intravenously inoculating rabbits and examining sections of organs from twenty-four hours up to several weeks, as well as by the introduction of cultures sealed in collodion capsules into the peritoneal cavity of rabbits. Wolbach stated that "the organism cannot be a blastomyces, neither can it be included in the oidium-like group of Ricketts, since the organisms of that group may reproduce by budding."

In 1907, Hektoen published a detailed review of cases and concluded that they were different diseases. In 1908, Montgomery and Ormsby summarized the literature, and, in 1909, Harter published a book on blastomycosis.

In the ARCHIVES OF INTERNAL MEDICINE, April 15, 1914, a series of eleven case-reports on systemic blastomycosis appeared, together with a pathological, bacteriological and clinical study of the disease by Stober. He obtained cultures from the moldy wood in the homes of the patients and noted a similarity with the cultures from human tissues. Vaccination with blastomycetes was tried in two systemic cases and one cutaneous case; of these one of the former patients

recovered. The vaccine consisted of the filtrate and suspension of the triturated membranes of old bouillon cultures which had been heated at 110 C. Stober inclines to the theory that systemic blastomycosis is primarily a respiratory infection. Blood cultures, in a case reported by Krost, Stober and Moes were positive. (Buschke had previously reported one such case.) The urine also showed blastomycetes, the source of which, as shown at necropsy, was the prostate. This series of articles consists of reproductions from the Cook County Hospital reports, 1910, as noted on page 509 of THE ARCHIVES.

The last summary of recently reported cases of coccidioidal granuloma together with experimental work has been published by MacNeal and Taylor. Anaerobic cultivation of the *Coccidioides immitis* in sterile ascitic fluid and gelatinized horse-serum with pieces of sterile tissue showed on inoculation of pus the development of round-cells and no filaments at the bottoms of the tubes. Such cultures have been kept alive for three weeks. Their work supports the observation of Wolbach that the double-contoured spheres in the animal tissues develop by a direct transformation of septate mycelial threads and not from the chlamydospores. MacNeal and Taylor believe that the disease produced by this organism is an entity and that it is differentiable from blastomycosis, oidiomycosis, etc., and that one point of practical therapeutic differentiation is the value of iodids in blastomycosis and their failure to benefit cases of coccidioidal disease, as emphasized earlier by one of us (Brown). MacNeal and Taylor conclude that coccidioidal granuloma is a definite specific infectious disease and that "*coccidioides immitis* (class *Ascomycetes*) is distinctly different from the budding fungi found in human diseases variously called blastomycosis, oidiomycosis," etc.

The association of coccidioidal granuloma and blastomycosis, as one disease, has been asserted by Wright, Ricketts, Buschke, etc., and a clinical confusion specifically illustrated by Morris' case of reported blastomycosis which was shown on laboratory examination to be coccidioidal disease. Welch believes that they are two differentiable diseases, and Ophüls, Hektoen, Wolbach, MacNeal and Taylor, and others, are of the opinion, as the result of clinical and laboratory observations, that they are separate conditions.

#### PERSONAL OBSERVATIONS

CASE 1.—H. D. V., aged 24, San Joaquin Valley, California, family and previous history negative, was in the Southern Pacific Hospital from Aug. 16 to 20, 1912, for laryngitis, which was suspected of being tuberculous, although reactions were negative. Readmitted with typhoidal symptoms. Widal positive 1:40 and blood-culture negative. Died March 2, 1913, having been in hospital about two months. Gross examination of organs revealed apparently a disseminated miliary tuberculosis, while microscopically coccidioidal lesions

were found in the spleen, lungs, liver, kidneys, pancreas and adrenals. The organisms showed endosporulation. There were no cultures.<sup>2</sup>

CASE 2.—Service of Dr. S. J. Gardner. J. P., aged 29, Mexican, laborer in section-gang (railroad), Bakersfield, San Joaquin Valley, Cal., was admitted to hospital July 27, 1913. Family history was negative. Patient denied venereal infection. The present infection apparently began three weeks before admission with a nodule on the dorsum of the right great toe. The day before admission it had been lanced and a quantity of pus escaped. He denied injury.

*Examination.*—Poorly nourished adult. Temperature was 104 F. and only a slight increase in respiratory and pulse-rates. Head, chest and abdomen negative. Right great toe presented two open wounds which were exuding considerable pus. Throughout the course of the disease the temperature fluctuated between normal and 104 F. The foot was kept for varying periods of time in a salt-water bath, and potassium iodid was administered internally in 20-grain doses thrice daily. There was no improvement and the patient was transferred to the roof that the foot might be exposed to the direct sun rays. For a time there was some decrease in the amount of pus. There was progressive decline, however, and about two weeks before death patient became stuporous, and had by this time become markedly emaciated. There was no apparent joint or other bone lesions and no evidences of pleurisy. No cough. Pus from the toe showed typical coccidioidal organisms with endosporulation. Tissue from margin of lesion showed the same. Blood: August 9, hemoglobin 70 per cent.; red blood-cells, 4,760,000; white blood-cells 16,600. Blood-cultures: August 6 and September 15, sterile. Urine: July 29, negative. Wassermann reactions: blood-serum, August 2, negative, and cerebrospinal fluid, September 10, weakly positive (++) . The fluid was moderately turbid and under a pressure of 140 mm. Butyric acid and ammonium sulphate reactions positive. Cells 20 (?) per c.mm.

*Necropsy Record.*—Markedly emaciated body. Bedsores over sacrum. Peritoneum smooth and dry and no adhesions. Spleen moderately enlarged (240 gm.). There were numerous small, firm, grayish nodules of millet-seed size. Liver slightly enlarged (1,620 gm.), dark brown and flabby. Gall-bladder apparently normal as well as stomach. Intestines were moderately congested. Pancreas apparently normal. Both kidneys moderately enlarged (from 200 to 210 gm.). Several millet-sized, whitish areas in cortex and medulla. Adrenals, ureters, bladder and genitalia apparently normal. In left pleural sac a few rather firm adhesions at apex. In left lung (500 gm.) numerous closely aggregated, grayish, firm nodules throughout both lobes. Right pleural sac normal. Right lung (620 gm.) resembled the left. Heart (300 gm.) had a pale, flabby muscle. Valves apparently normal. Beginning of aortic arch showed few small areas of early sclerosis. Retroperitoneal lymph-nodes moderately enlarged and firm. Brain (1,360 gm.) showed a uniformly moderate thickening of the dura mater. Overlying the occipital dura there was a well defined purulent collection which was directly continuous through a necrosed portion of the occipital bone with a larger mass of pus beneath the scalp. There was early necrosis of the left temporal bone. There was extensive necrosis of the upper half of the sternum and the third, fourth and fifth lumbar vertebrae with pus development, as well as the bones of the right great toe.

Microscopic examination showed coccidioidal lesions (endosporulating organisms) in the lungs, liver, kidneys, occipital bone, dura mater, meninges of cervical and dorsal cord, as well as congestion, edema, emphysema and hemosiderosis of lungs; passive congestion of liver, congestion of adrenals, chronic gastro-enteritis, chronic retroperitoneal lymph-adenitis; hyaline changes in right soleus muscle.

2. Carson and Cummins: A Case of Coccidioidal Granuloma (California Disease), Jour. Am. Med. Assn., 1913, lxi, 191.

Cultures made at necropsy and incubated at 37 C. showed within twenty-four hours growth of coccidioidal organisms.

CASE 3.—Service of Dr. J. H. O'Connor. A. R., aged 27, blacksmith helper, Kerto (since August, 1913), San Joaquin Valley, Cal., was admitted to Hospital March 5, 1914. Family and previous personal history negative. Patient denied venereal infection. The present condition apparently began ten days previously with lumbar pains. Patient *stated that he lost about 13 pounds in fifteen days.* He denied injury.

*Examination.*—Fairly well-nourished man. On admission temperature, pulse and respiration normal. No tenderness in lumbar region. Blood-pressure, systolic, 120 mm. Urine, negative. Two days after admission there was definite localization of tenderness, and a mass noted in the lumbar muscles over the left kidney. On opening there exuded considerable pus in which double-walled endosporulating cells were found. Six weeks after admission, tenderness and swelling of the right wrist and left elbow appeared. At that time there was a moderate purulent discharge from the lumbar lesion, whose walls were of a gray, slimy, necrotic appearance. The Roentgen picture showed no apparent connections with the spine. Throughout the period of illness an irregular temperature was maintained; maximum was 103.4 F. Daily applications for five minutes of gauze saturated with pure phenol were made over a period of seven weeks. Then for four weeks daily applications to the lesion of gauze saturated with 0.25 per cent. solution of crystal violet were made. At no time were there evidences of granulations nor, on the other hand, extended necrosis. During the latter period intravenous injections of crystal violet were given, as follows:

May 8, 100 c.c. of 0.25 per cent.; May 11, 100 c.c. of 1 per cent.

May 16, 100 c.c. of 2 per cent.; May 19, 400 c.c. of 4 per cent.

Slight chills following three injections were probably induced by insufficient heating of the solution rather than by any toxicity of the crystal violet. On May 13, 5,200 c.c. of violet-tinged ascitic fluid were withdrawn; on May 21, 2,250 c.c.; on May 28, 1,040 c.c. The swelling of the wrist and elbow decreased and there was no other apparent bone or joint involvement. Death, June 1. Unfortunately permission for necropsy could not be obtained.

#### EXPERIMENTAL WORK

The coccidioidal cultures used for animal inoculations and bacteriological study were those from Case 2; the blastomycosis culture was obtained from a systemic case at the city and county hospital through the courtesy of Dr. Harold Hill. A limited bacteriological study was carried out on the strain of coccidioides from Case 3. Other cultures of coccidioides were obtained from Dr. Cook of the University of California and from Drs. MacNeal and Taylor of the Post-Graduate Medical School in New York, and form the basis of study which is not yet completed. Rabbits, guinea-pigs and white rats were inoculated with the coccidioides and blastomycetes, and cats with the coccidioides only.

#### COCCIDIOIDES

##### *Five Rabbits*

*Rabbit 1.*—December 13: Inoculated *intravenously* 2 c.c. salt solution suspension culture containing spores.

December 29: Killed. Coccidiosis liver. No evidence of coccidioidal disease.

*Rabbit 2.*—December 13: *Intraperitoneally* 5 c.c. salt solution suspension of culture.

December 29: Killed. Coccidiosis of liver. No evidence of coccidioidal disease.

*Rabbit 3.*—December 13: *Intrapleurally* as Rabbit 1. December 16 and December 22 negative.

January 5: Pea-sized mass near site of inoculation, but not attached to ribs.

January 23: Chestnut-sized mass.

April 4: Killed. Large mulberry-form abscess intrathoracic at site of inoculation. Small abscess extrathoracic. Left ankle-joint enlarged and contained some pus; at right knee small firm tumor. Coccidioidal organisms in pus.

*Rabbit 4.*—December 13: *Intratesticularly* (right) as 1. Small bead in epididymis.

December 22: Both testicles enlarged and right indurated.

January 5: Sinus from right.

January 23: Both testicles size of small lemons. No discharge from sinus.

February 28: Killed. Purulent orchitis (bilateral); coccidioidal organisms in pus.

*Rabbit 5.*—December 13: *Inguinally* (right) as Rabbit 1.

December 16 and 22: Negative.

January 5: Split pea-sized nodule in groin.

January 23: Lima-bean-sized nodule at seat of inoculation.

March 18: Killed. Purulent arthritis of left shoulder and right elbow. Pus showed coccidioidal organisms.

*Summary.*—*Intrapleurally*, *intratesticularly* and in inguinal region, positive. *Intravenous* and *intraperitoneal* inoculations, negative.

#### *Nine Guinea-Pigs, Male*

*Pig 1.*—September 3.—Inoculated *intraperitoneally* with 2 c.c. salt solution suspension of pus from Case 2.

September 22: Both testicles somewhat enlarged.

October 2: Sinus from each testicle.

October 21: Killed. Coccidioidal lesions of testicles and spleen.

*Pig 2.*—September 3: Inoculated as above.

October 27: Indurated ulcer of scrotum.

October 29: Also enlarged right inguinal nodes.

December 4: Testicle healed; inguinal enlargement persisted.

December 16: Died. Coccidioidal involvement of inguinal nodes only.

*Pig 3.*—September 3: Inoculated as above.

October 27: Both testicles somewhat enlarged.

October 7: Small indurated ulcer of scrotum.

October 29: Also enlarged inguinal nodes, both sides.

December 4: Killed. Large mass in left inguinal region. Some enlargement of axillary groups in both sides. Coccidioidal disease present.

*Pig 4.*—November 24: Inoculated with 4 c.c. salt solution suspension 4 months'-old culture *intraperitoneally*. December 4. Some induration of both testicles.

December 12. Also slight inguinal enlargement.

December 16: Died. Coccidioidal lesions in left inguinal node and testicle.

*Summary.*—*Intraperitoneal* inoculations positive.

*Pigs 5, 6, 7 and 8.*—December 18: Each inoculated *intraperitoneally* with 1 c.c. salt solution suspension of pus from testicle of Pig 4.

December 21-22: All died. Congestion of lungs, liver, kidneys and adrenals. Cultures from peritoneal fluid sterile.



*Pig 9.*—December 21: Inoculated *intraperitoneally* 1 c.c. salt solution suspension of peritoneal exudate from one "December 18 pig."

December 25: Died. Congestion heart, kidneys, lungs and liver. Cultures from peritoneal fluid sterile.

#### *Thirteen White Rats*

*Rat 1.*—September 6: Inoculated *subcutaneously* in back with 1 c.c. salt solution suspension pus from Case 2.

March 22: Ulcer at site of inoculation.

October 2: No pus—more induration.

October 19: Died. Negative.

*Rats 2 and 3.*—September 6: Inoculated *intraperitoneally* as above.

September 14: Some redness and swelling at sight.

October 2: Some induration of testicles.

November 12: Negative.

January 20: Killed. Negative.

*Rat 4.*—November 24: Inoculated *intraperitoneally* with salt solution suspension of 4-months-old culture.

December 4: Small nodule at site of inoculation.

January 5: Negative.

April 4: Killed. Small firm cysts in liver. *Coccidioides* in smears and cultures.

*Rats 5, 6 and 7.*—March 5: Inoculated *intraperitoneally* with 1 c.c. salt solution suspension of pus from testicle of Rabbit 4. Killed March 17 and one only showed coccidioidal organisms in fluid from small hepatic cyst.

*Rats 8, 9 and 10.*—March 5: Inoculated as above.

April 17: Killed. All negative.

*Rats 11, 12 and 13.*—March 5: Inoculated *testicularly* as above.

April 17: Killed. All negative.

*Summary.*—Two of thirteen rats, positive.

#### *Five Cats*

*Cat 1.*—Full grown. September 5: Inoculated *intraperitoneally* with 2 c.c. salt solution suspension pus from Case 2.

September 14: Some swelling at site of inoculation.

September 18-27, October 2: Idem.

October 15: One area size of quarter dollar and several smaller areas.

October 22: Idem.

November 15: One large area of induration.

December 4: Small nodule.

December 12: Idem.

January 5: Negative.

January 28: Killed. All organs grossly negative. Microscopically, few coccidioidal organisms found in small dense cellular collections in lungs.

*Cat 2.*—Full grown. September 5: Inoculated *subcutaneously* in back as above.

September 14: Some swelling at site of inoculation.

September 18 and 27 and October 2: Idem.

October 7: Small area of induration.

October 22: Area of fluctuation.

October 29: Ulcer. Coccidioidal organisms in smears.

November 5: Ulcer healing.

December 4: Ulcer healed.

December 12: Negative.



January 28: Killed. Few small whitish nodules in liver. Smears negative. Other organs including brain and cord grossly negative. Microscopically few coccidioid organisms in lungs as above.

*Cat 3.*—Kitten. September 14: Inoculated *intraperitoneally* with 2 c.c., as above.

January 28: Killed. All organs grossly and microscopically negative.

*Cat 4.*—Kitten. September 18: Inoculated *intraperitoneally* as above.

September 22: Negative.

September 27 and October 2: Two pea-sized masses at site of inoculation.

October 7 and 22: Moderate increase in size.

November 15: Negative.

January 28: Killed. All organs negative grossly and microscopically.

*Cat 5.*—Kitten. September 18: Inoculated *subcutaneously* in back. At above dates of examination negative.

January 28: Killed. All organs negative grossly and microscopically.

*Summary.*—Full-grown cats, positive. Kittens, negative.

#### BLASTOMYCETES

##### *Four Rabbits*

*Rabbit 6.*—December 13: Inoculated *intraperitoneally* with 5 c.c. salt solution suspension of 5-months-old culture.

December 16 and 22: Negative.

January 5: Abdomen somewhat boggy.

January 23: Killed. No evidence of blastomycosis.

*Rabbit 7.*—December 13: Inoculated *inguinally* as above.

December 16: Negative.

December 22: Died of pneumonia. No evidence of blastomycosis.

*Rabbit 8.*—December 13. Inoculated *intrapleurally* with 5 c.c. as above.

December 22 and 23, January 5 and 23, April 16: Negative.

April 17: Killed. No gross evidence of blastomycosis.

*Rabbit 9.*—December 13: *Intratesticularly* (right) with 0.75 c.c. as above.

December 16: Some swelling of the testicle.

January 5: Testicle as large as a lime.

April 16: Apparently normal.

April 17: Killed. Tunica vaginalis testis contained two split-pea-sized nodules containing thick pus in which blastomycetes (budding forms) were found. Right lower eyelid was covered with thick pus and small papillary projections were noted when pus was removed. Blastomycetes were found in pus.

*Summary.*—Intratesticular inoculation positive. Intrapleural, inguinal and intraperitoneal inoculations negative.

##### *Three Guinea-Pigs, Male.*

*Pig 10.*—November 24: Inoculated *intraperitoneally* with 4 c.c. salt solution suspension of 4-months culture.

December 22: Boggy abdomen.

Dec. 26: Died. Congestion of liver and kidneys. Abscess in right epididymis containing drop of pus. Blastomycetes in smears and cultures.

*Pig 11.*—December 27: Inoculated *intraperitoneally* with 2 c.c. salt solution suspension of pus from epididymis of Guinea-Pig 10.

January 13: Died. Congestion of lungs and liver; acute nephritis; acute follicular splenitis. No blastomycetes.

*Fig 12.*—Inoculated as *Fig 11*.

April 17: Killed. No evidence of blastomycosis.

*Summary.*—Two of three intraperitoneal inoculations negative.

#### *White Rats*

*Rat 14.*—Inoculated *intraperitoneally* with 2 c.c. salt solution suspension of 4-months-old culture.

December 4: Small nodule at site of inoculation.

April 4: Killed; negative.

#### GENERAL SUMMARY OF ANIMAL INOCULATIONS

White rats seem to be markedly insusceptible to infection with coccidioides and blastomycetes; cats to coccidioides. Rabbits and guinea-pigs appear to be more susceptible to coccidioidal than to blastomycetic infection. No lesions were found in the cerebrospinal tissues. Passage through animals would seem to exalt the virulence of coccidioides as shown by five guinea-pigs (5, 6, 7, 8 and 9).

#### CULTURAL STUDIES

Both coccidioides and blastomycetes grew well on agar of strongly acid and alkaline reactions. Dextrose, dextrin, lactose, saccharose, maltose, raffinose, mannite, galactose, esculin, sorbit, agaricin, rhamnose, adonite, xylose, arabinose, mannose and salacin were not fermented by the coccidioides or blastomycetes. The addition of potassium iodid to mediums for facilitating the growth of the coccidioides or blastomycetes by inhibiting the growth of contaminating bacteria, was not employed in the isolation of the organisms from pus, as it was found that after a short time they overgrew the bacteria.

It was noted that the blastomycetes tubes incubated at 37 C. did not grow so well or so rapidly as when they were kept at room temperature. This fact has been called attention to by Ophüls, whose further statement that coccidioides grows best at 37 C. we also confirm.

Of fifty dyes in neutral agar the violets uniformly showed the greatest inhibitive action on the coccidioides, blastomycetes and staphylococci, and the greens ranked second. The blue dyes varied considerably from the strongest, methylene blue BX and brilliant cresyl blue to the weakest, trypan blue and china blue. Such dyes as safranin, congo red and victoria blue showed well marked differences in their action on the respective organisms. A relatively marked inhibition was effected by safranin on staphylococci. The reverse was true of congo red. Victoria blue exerted a well marked inhibition of the growth of blastomycetes and no inhibition of the coccidioides and staphylococci. Purpurin, orange G, rubin S, sudan III, methyl red, etc., were quite inert. (Some poorly soluble.) Uniformly, the most inhibitive dye was

TABLE 1. REACTIONS OF STAPHYLOCOCCI, BASTOMYCESES AND COCCIDIUMS WITH VARIOUS DYES OF DIFFERENT STRENGTHS.\*

	0.0005	0.001	0.0025	0.005	0.01	0.02	0.05	0.1	0.25	0.4	0.5	0.6	0.75	0.9	1.0	1.25	1.5	1.75	2 c.c.	
	0.01%	0.02%	0.05%	0.1%	0.2%	0.4%	0.1%	2%	5%	8%	10%	12%	15%	18%	20%	25%	30%	35%	40%	
VIOLET DYES																				
Crystal Field Violet	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Crystal Violet	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fuchsin	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gentian Violet	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hoffmann's Violet	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Methyl Violet 1 B	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Methyl Violet 2 B	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Methyl Violet 3 B	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Methyl Violet 4 B	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Methyl Violet 5 B	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Methyl Violet 6 B	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Methyl Violet 6X	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Resorcin Violet	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
GREENS																				
Brilliant Green	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

\* Explanation of abbreviations in table: B, blastomyces; C, coccidioides; S, staphylococcus (from a case of osteomyelitis). 5 c.c. neutral agar per tube. Serialized aqueous solution of dyes from which serial percentages (0.01 to 40) were made. Tubes autoclaved for twenty minutes.

TABLE 1.-(Continued)



TABLE I. Continued.



crystal violet, but for the blastomycetes methyl violet 1 B and 6 B. Crystal violet and Hofmann violet were of equally high potentiality for the coccidioides and blastomycetes. Intraperitoneal inoculations of aqueous solutions of crystal violet in 0.25, 0.5, 1 and 2 per cent. concentration into guinea-pigs and white rats produced no toxic effects. As before noted, this dye was made the basis of therapy in Case 3. Safranin agar in 10 to 20 per cent. strength may prove of value in the isolation of coccidioides from pus and in 10 to 15 per cent. strength, in the isolation of blastomycetes.

The primary growths of the coccidioides from Cases 2 and 3 required two to ten days for their appearance, except in the former, in which a few tubes of slant agar were thickly streaked with pus, and growth appeared within twenty-four hours. There is a tendency primarily for the pyogenic organisms to outstrip the coccidioidal growth, but in the course of two weeks the former growth is practically obliterated. After several subculturings of Strain 2, growth appeared in twenty-four hours. This strain showed the initial characteristic of fine, white threads radiating out over the agar surface, while that from Case 3 showed a whitish "cottony" surface without such radiations. As the agar slants became covered with growth, both strains assumed a somewhat dry, wrinkled, fleshy, brownish-white appearance. Especially in Strain 2 there was early penetration of the agar, and in the thinner drier portions of the medium (top of slant) there was an early development of the whitish "cottony" growth. This appearance was not general until the cultures became old and dry. Strain 3 has not been studied sufficiently long to determine this point. In both strains the growth after a time was of irregular thickness, being in places somewhat elevated and densely adherent to the medium, so that it was necessary for subinoculation to remove small pieces of agar. Strain 2 on the "dye-agars" developed in many tubes well-marked aerial hyphae as a primary growth. With some dyes, notably eosin, orange G and the rosanilins, general growth was more rapid and luxuriant than on the plain agar. Those cultures developed early the whitish, dry, "cottony" growth in dense masses projecting from the surface of the medium. All tubes were incubated at 37 C.

Early in the period of subculturing our strain of blastomyces, seven to ten days elapsed before there were evidences of growth, but later in many tubes this period was reduced to two or three days. The primary growth in all plain agar slants consisted of round, moist, flat colonies composed of radiating whitish lines. Later coalescence took place and the surfaces dried and cultures assumed the appearance as described by Ricketts "(3) aerial hyphae and surface white, dry and flour-like and eventually covering sides of tube." For subinoculation

this growth could easily be removed without puncturing the agar. The eosin, orange G and rosanilin agars favored luxuriant growths. On practically all of the dye-agars primary growth was manifested by aerial hyphae. All tubes were kept at room temperature.

Microscopically, both the coccidioides and blastomycetes in animal tissues presented the characteristic endosporulation and budding processes, respectively. Neither in the pus nor in the solid tissues at any time could we demonstrate budding forms in coccidioidal disease, nor evidences of ensporulation in blastomycosis. No mycelia were found in the tissues in either disease. In cultures of both types of organisms, the already well-described cylindrical, septate, branching filaments with later spore development were noted. Agar slides, as described by Wolbach, were used to study the development of filaments from the cells as found in pus. We found the most satisfactory stain of the culture material to be eosin and methylene blue, but in pus the cells were readily studied on adding a dilute (4 per cent.) caustic soda solution.

The initial growth of coccidioides on culture mediums is rapid, for, if a quantity of pus is inoculated, growth in some tubes has been noted within twenty-four hours. Blastomycetes require in their initial growth about ten days to two weeks for evidence of definite development, but after prolonged cultivation growth is seen in four to seven days. The optimum temperature for coccidioides is 37 C., and for blastomycetes about 20 C. Some strains of blastomycetes eventually show luxuriant growth to the extent that the sides of the container are invaded, whereas the growth of coccidioides seems always to be confined to the mediums.

Animal inoculation yielded well-defined endosporulating organisms of coccidioidal disease, and in the pus of blastomycosis only the budding forms.

#### SUMMARY

There are well-defined differences in the pathogenicity of the two diseases, coccidioidal granuloma being always fatal, and often rapidly fatal in man, while blastomycosis is commonly not so, except for the systemic cases, in which the organisms were found associated with bacteria of known and unknown pathogenicity (Zinsser, Hektoen, Gilchrist and Stokes). The clinical and pathologic aspects of coccidioidal disease are those more closely resembling tuberculosis, as there is a greater predilection for the lymphatic system than there is in blastomycosis, and cutaneous lesions are likely to be more ulcerative. There appears but one reported case of coccidioidal disease in the female sex, whereas there have been many of blastomycosis. Iodids have temporarily benefited many, and apparently cured a few, blasto-

mycosis patients, whereas they have had no effect on the rapidly progressive lesions and toxemia of coccidioidal granuloma.

In the reported cases of coccidioidal granuloma and blastomycosis confusion is common as to clinical, pathological and bacteriological characteristics. The two organisms appear closely related, having much in common, but with such differences as to justify the conclusion that they are distinct entities. Morphologically, in pus and solid tissues they are differentiable by the endosporulation in the one and budding in the other. Cultural differences are not so pronounced, although we have found that growth is initially more rapid with coccidioides. Blastomycetes appear to grow best at room temperature (20 C.); coccidioides at 37 C. The table of dyes shows some differences in the inhibition of growth. Rabbits and guinea-pigs are more resistant to blastomycetic than to coccidioidal infection.

These appear to be sufficient reasons to justify the consideration of coccidioidal disease and blastomycosis as two different diseases. A second paper will deal with the diseases from serological, vaccine and chemotherapeutic points of view.

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## THE SPECIFIC GRAVITY OF THE HUMAN BODY \*

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### HISTORICAL

Specific gravity is one of the first fundamental principles of hydrostatics, and its discovery is ascribed to Archimedes (287 B. C.). The incentive to his discovery and the method of his reasoning is described in the following story which carries with it the flavor of the East:

King Hiero ordered his silversmith to make for him a crown of pure gold. When the crown was brought before him he suspected the honesty of the silversmith, and desired to know if Archimedes could devise a way of testing the question without injuring the crown. The philosopher pondered the problem for a long time without succeeding, but one day as he stepped into a bath his attention was attracted by the overflow of water. A new train of ideas was started in his ever receptive brain. Wild with enthusiasm he sprang from the bath, and forgetting his robe, he dashed along the streets of Syracuse shouting "Eureka! Eureka!" The thought that came to his mind was this: that any heavy substance must have a bulk proportionate to its weight, bulk for bulk, and that the way to test the bulk of such an irregular object as a crown was to immerse it in water. The experiment was made. A lump of pure gold of the weight of the crown was immersed in a certain receptacle filled with water and the overflow was noted. Then a lump of silver of the same weight was similarly immersed. Lastly, the crown itself was immersed, and of course — for the story must not lack in dramatic sequel — was found bulkier than its weight of pure gold. The silversmith confessed that he made the crown of an alloy of silver and gold. The historian of science<sup>1</sup> traces the first record of this story to the tenth century, but the principles of specific gravity have fortunately been tersely and lucidly stated by Archimedes himself in his book on floating bodies.<sup>2</sup>

### DEFINITION

Specific gravity is the ratio between the weights of equal volumes of any substance and of some other, chosen as a standard. For solids and liquids, distilled water at 62 F. and barometer 30 is taken as a standard.

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1. Cajori: *History of Physics*, 1899, p. 4.

2. *Works of Archimedes*, edited by T. L. Heath. Cambridge University Press.



According to the law of Archimedes, a solid floating or immersed in a liquid loses weight equal to that of the volume of liquid it displaces, hence,

$$\frac{\text{Weight of solid}}{\text{Loss of weight}} = \frac{\text{Specific weight of the solid}}{\text{Specific weight of the liquid}}$$

And, since the specific weight of the liquid is unity, hence

$$\text{The specific gravity of the solid} = \frac{\text{Weight of solid}}{\text{Loss of weight}}$$

In other words, the specific gravity of the solid equals its own weight divided by the weight of the volume of liquid it displaced.

#### THE PIONEERS: OBSERVATIONS ON THE SPECIFIC GRAVITY OF SEPARATE ORGANS OF THE HUMAN BODY

The older anatomists and physiologists paid considerable attention to the study of the specific gravity of the different organs of the human body.<sup>3</sup> John Davy<sup>4</sup> (1828) made careful observations on the specific gravity of some eighty different tissues and organs and he expressed the hope "that the physiologist will receive them as a contribution to his science, and that the pathologist may derive from them a help to the eye and a more certain criterion of organic change than we yet possess. . . . The results are almost demonstrative that organic diseases of the viscera cannot take place without altering their specific gravity; and if it is so, it is not improbable that this precise quality may be made an index of the kind and degree of organic changes."

As far as the available literature at my disposal goes,<sup>5</sup> the credit of the earliest record of observations on the specific gravity of the human body belongs to John Robertson<sup>6</sup> (1814), librarian of the Royal Society. He constructed a cistern 72 inches (183 cm.) long, 30 inches (76 cm.) wide and 30 inches (76 cm.) deep, and having procured ten men for his purpose, the height of each was taken and his weight, and afterward they plunged successively into the cistern. A rule or a scale graduated to inches and decimal parts was fixed to one end of the cistern, and the height of the water shown was noted before each man went in, and to what height it arose when he immersed himself under its surface.

One of the reasons, Mr. Robertson says, that induced him to make these experiments was a desire to know what quantity of timber would

3. See bibliography, *Specific Gravity of Separate Parts of the Human Body*, at end of article.

4. Davy, John: *Trans. Med. Soc., Edinburgh*, 1829, iii, 436; also in *Researches, Physiological and Anatomical*, London, 1839, ii, 253.

5. See bibliography *Specific Gravity of the Human Body* at end of article.

6. Robertson, John: *Philosophical Transactions*, 1, Art. 5. Quoted in *Hutton's Philosophical and Mathematical Dictionary*, London, 1815. (Article, *Specific Gravity*.)

be sufficient to keep a man afloat in water, thinking that most men were specifically heavier than river or common fresh water; but the contrary appears from trials made, for except the first, every man was lighter than an equal bulk of fresh water and much more so than sea water, so that, "if a person who falls in water had presence of mind enough to avoid the fright usual on such occasions they might be preserved from drowning, and a piece of wood no larger than an oar would buoy a man partly above water as long as he had strength or spirit to keep up his hold."

One hundred years have passed since Robertson made his crude experiments, and yet the number of observers who followed him can be counted on the fingers of one's hands, and the number of observations barely reach the two hundred mark, including the experiments made on cadavers (Herman<sup>7</sup>). Nevertheless these pioneers deserve our gratitude for having established a few definite and valuable facts in connection with this interesting but neglected study, and especially for having discarded the crude contrivance of Robertson's wooden box-cistern in which the material, the shape and the size gave rise to innumerable sources of error, to which we will refer later.

#### THE AUTHOR'S SPECIFIC GRAVITY APPARATUS

*The Volumometer.*—The tank is constructed of sheet iron, cylindrical in shape, 64 cm. in diameter and 165 cm. in height. The vessel is reenforced by a steel hoop at about its middle. To avoid injury to the subject while entering and leaving the tank, the sharp upper brim is flanged. The level of the water in the tank is indicated on the water-gage made of Scotch glass, 3 cm. in diameter, graduated in centimeters and millimeters. By means of a rubber tube attached to the water-supply, cold and hot water<sup>8</sup> can be poured into the tank and the temperature tested and regulated either by the tactile sense or by using a water thermometer. The tank is emptied through the outflow pipe attached to the lower end of the water-gage. To dispel the fear of entering a dark reservoir, an electric lamp with a strong reflector illuminates the interior of the tank. After the experiment, if necessary, the tank can be sterilized. To facilitate thorough draining, the tank is placed on a wooden block four inches thick. The entering and the leaving of the tank is facilitated by the use of suitable stepladders. It

7. Herman: Quoted by Buhl in Mitt. a. d. Pathol. Inst. z. München., 1878, p. 4.

8. The quality and temperature of the water have no appreciable influence on its specific gravity. The specific gravity of water at 4 C. is 1.000, and at 40 C. is only 1.00757 (Rossetti, Poggendorff's Ann. d. Physik u. Chemie., 1871, v., 268). The difference between distilled water and any other fresh water is nil.

need not be remarked that during the experiment the tank contains nothing but water and the body whose specific gravity is to be determined.

*The Computation of the Content of the Volumometer.*—The solid content of a cylinder is computed according to the well-known formula,  $\pi r^2 h$  (in which  $\pi$  represents circumference,  $r$  radius and  $h$  height). The diameter of our tank being 64 cm., the radius is 32 cm. The circumference  $\pi$  is 3.14. Therefore the content of each longitudinal



The volumometer, an apparatus for determining the specific gravity of the human body.

centimeter of the tank ought theoretically to be  $3.14 \times 32 \times 32 \times 1 = 3,215$  c.c. (decimals omitted). On carefully measuring our tank by filling it with water from a graduate and noting the number of cubic centimeters it required to raise the level 1 cm., it was found that each centimeter gave a slightly different reading, but each ten centimeters throughout the whole height of the tank gave the same reading, namely, 3,240 c.c., the difference between the theoretical formula and the actual measurements being only 25 c.c. As the difference is practically a negligible quantity, the value of 3,240 c.c. for each centimeter of the tank was used in my calculations.

## WHERE DOES THE GAIN OR LOSS IN BODY WEIGHT GO?

All previous investigators had one end in view, namely, to find by means of the difference in the specific gravity the change in the increase or the diminution of the bulk of the body as compared to the weight. A man weighing, say 176 pounds, when immersed in the tank displaces 79,380 c.c. of water. His specific gravity will be 1.006. Later the man was found to have gained 10 pounds. He has increased in bulk and consequently he should displace a larger volume of water. This is found to be so. He displaces 84,000 c.c. His specific gravity is now 0.990. Or, in other words, when the man weighed 176 pounds he was heavier than water; now that he weighs 10 pounds more he is lighter than water. Since the specific gravity of all tissues except fat<sup>3</sup> is higher than water, if the increase had been due to the enlargement of the muscular or bony tissues his specific gravity would have been the same or higher than before. But the specific gravity has been found lower and therefore it is evident that the increase in his bulk was primarily due to an increase in his fatty constituents. Such a procedure is of diagnostic value.

It was my endeavor, however, to solve an entirely different problem. Let us take the case above referred to of the man having gained 10 pounds; the question arises: How can we locate the gain? In other words: How have the 10 pounds distributed themselves over the body? Have they spread themselves uniformly through the body or not? If the additional bulk has not been distributed uniformly, is there a definite relative increase in the various sections of the body? Have 3 pounds been added to the upper extremity and 7 pounds to the lower extremity, or vice versa? The same question is of course applicable to a man who has lost 4,536 kg. (10 pounds). As far as I could trace, not only has there never been made an attempt to solve this problem, but it has never even been propounded.

In order to arrive at a solution, I reasoned as follows: A human body, being immersed to the knees, will displace a certain volume of water, say 5,000 c.c. The same man immersed to the arch of the pubic bone will displace 15,000 c.c. Immersed to the arch of the ribs, he will displace 50,000 c.c. It is evident that the volume of his feet and legs will be 5,000 c.c., the volume of his thighs will be 10,000 c.c., and the volume of his abdomen from the pubic bone to the arch of the ribs will be 35,000 c.c. After the man has gained 10 pounds he is again immersed in the tank and the same measurements taken. All the readings will show a perceptible change, from which the calculation as to the relative increase in volume can easily be ascertained.

AUTHOR'S METHOD OF TAKING THE VOLUMETRIC MEASUREMENTS OF  
THE HUMAN BODY

Before the experiment begins the subject should undergo a physical examination. Any deviation from the normal should be noted. The bowels should have moved on that day and the urine be voided before the experiment. I have limited the measurements to the following: (1) the height; (2) the circumference of the chest at the nipple line in normal breathing; (3) the circumference of the abdomen at the umbilical line; (4) the spread of the arms from the tip of the fingers of one hand to the tips of the other hand; (5) the distance from the umbilical line to the floor; (6) the distance from the nipple line to the floor; (7) the distance from the prominence of the thyroid cartilage to the floor.

Immediately preceding the entrance into the tank, the subject should be carefully weighed. The tank is filled to the level of 70 cm. with warm water at a temperature of about 80 F. The subject climbs on the step-ladder and descends into the tank on a small ladder, which hangs on hooks from the rim of the tank. The small ladder is then removed. The level of the water in the tank is indicated on the water-gage. As we know the distance from the umbilicus to the floor, we can readily bring the level of the water to the umbilical line either by adding or letting out a certain quantity of water. The level of the water at the umbilical line is then noted. The small ladder is again introduced into the tank and the subject leaves the tank. The level of the water in the tank is noted. Deducting the second reading from the first gives the number of centimeters which the section of the body from the umbilicus down has raised in the tank. Multiplying this number of centimeters by 3,240 (cubic centimeters to 1 cm. height of tank) gives the number of cubic centimeters which the volume of the body from the umbilical line down displaced. More water is poured into the tank, say to the level of 90 cm. The subject again enters the tank and the level adjusted to the measurements of the nipple line as per measurements made before the experiment began, and the level on the water-gage noted. The subject leaves the tank and the lowered level is again noted. The second reading is subtracted from the first and the difference multiplied by 3,240 and thus the number of cubic centimeters displaced by the volume of the body from nipple line down is obtained. Subtracting from this the number of cubic centimeters obtained from the displacement of the body from umbilical line down we get the amount of water displaced by the volume of the body from the nipple line to the umbilical line. The same is repeated for the section of the body from the prominence of the thyroid cartilage to the nipple line.

TABLE OF AUTHOR'S OBSERVATIONS ON THE SPECIFIC GRAVITY OF THE ENTIRE BODY AND ON THE SPECIFIC EQUIVALENT OF CERTAIN PARTS OF THE BODY

No.	Age	Weight, Kg.	Height, Cm.	Chest, Cm.	Abdo- men, Cm.	Span of Arms, Cm.	Head		Neck to Nipple		Nipple to Umbilicus		Umbilicus to Floor		Entire Body	
							Volume, C.c.	Equivalent, Sp. Gr.	Volume, C.c.	Equivalent, Sp. Gr.	Volume, C.c.	Equivalent, Sp. Gr.	Volume, C.c.	Equivalent, Sp. Gr.	Volume, C.c.	Specific Gravity
1	32	78.956	145	100	100	174	3,888	22,1065	.....	3,0699	.....	.....	.....	.....	76,280	0.964
2	32	78.172	145	100	.....	174	3,888	20,1374	21,284	3,2870	11,904	5,2702	26,222	2,6522	78,408	1.000
3	32	78.019	.....	100	.....	.....	.....	20,0065	56,721	3,7003	.....	.....	.....	.....	76,788	1.017
4	30	66.679	171	84	79	178	3,740	20,5739	14,256	4,6772	18,054	3,6877	20,456	2,4226	66,696	1.008
5	28	66.225	168	93	85	173	4,336	14,829	20,088	3,2967	11,664	5,6662	28,836	2,2966	65,124	1.016
6	19	32.577	134	.....	.....	.....	.....	.....	.....	.....	10,778	5,6673	28,742	1,8449	53,436	0.985
7	15	29.090	146	76	66	155	3,240	14,5500	19,212	3,3500	8,748	4,3338	19,416	2,0746	43,416	0.946
8	15	49.415	154	73	72	139	3,565	13,800	10,043	4,4004	8,748	5,6633	24,248	1,9757	47,204	1.010
9	14	40.824	141	71	66	.....	3,565	11,4363	8,747	4,0670	8,460	5,0400	20,088	2,6222	40,560	1.008
10	11	34.173	141	66	62	143	3,946	11,8990	6,480	5,0411	7,128	4,8962	15,472	2,0075	33,696	1.029
11	14	33.329	139	65	58	143	3,175	10,7067	.....	.....	.....	.....	15,622	2,1437	34,772	1.049
12	13	30.164	135	63	62	139	3,210	9,0001	6,156	.....	6,480	4,6540	14,556	2,1158	30,432	1.001
13	12	29.037	141	67	58	138	2,562	11,5497	6,280	4,8969	5,632	5,0409	14,580	2,6532	29,484	1.010
14	11	31.798	137	63	59	141	2,946	10,9004	7,678	4,7049	6,480	4,7966	14,904	2,4365	30,780	1.038
15	9	21.071	.....	61	61	.....	.....	.....	4,800	4,8040	.....	.....	.....	.....	.....	.....
16	8	26.302	174	60	59	.....	.....	.....	.....	.....	.....	.....	11,340	.....	27,216	0.976



The last measurement, that of the head, is taken with the body immersed to the level of the prominence of the thyroid cartilage. The subject is told to hold his breath and duck slowly under the water, the assistant watching that head is completely under water. The oscillation of the column in the water-gage will go on for a while and settle in a few seconds. The observer at the water-gage notes the level and taps on the tank which is distinctly heard by the subject and is a signal that the experiment is at an end and that he may stand up. In my experiments I had every subject repeat the last procedure two or three times and the reading was found to differ in from 0.1 cm. to 0.2 cm. in some cases, and in others not at all. Of course it is interesting and highly instructive to take note also of the volume of the water displaced in deep inspiration and complete expiration, and compare it with the displacement during normal breathing. The whole procedure lasts from twenty to thirty minutes.

#### REMARKS ON THE AUTHOR'S EXPERIMENTS

The volumetric measurements were taken of fourteen individuals, four adults (three males and one female) and ten boys, ranging in ages between 53 and 8 years; in weight from 79 kg. to 26 kg., and in height from 1.71 meters to 1.35 meters. All the measurements were taken at 7 p. m. before the evening meal. The specific gravity of the entire body ranged between 0.976 and 1.049. The average specific gravity of the adults was 1.003, and of the boys 1.006. The average specific gravity of all individuals examined was 1.005. One of the subjects was placed on a certain diet and his displacement measured every other day, when he weighed 175, 174 and 173 pounds, respectively.<sup>9</sup>

As all my predecessors have made their experiments solely for the purpose of taking the specific gravity of the entire body, and therefore each person examined had nothing else to do on entering the filled tank but to immediately duck his head under the water, the observers encountered many difficulties which undoubtedly caused many errors in the calculations. The difficulty arises in having the subjects dip their heads during normal breathing. The tendency is, in the majority of cases, to take a deep inspiration, and, in a few cases, to make a complete expiration, before plunging. In the former case the reading will be too low, and in the latter case, too high. The subjects are frightened, anxious, excited. Not so with my method. The individual enters the bath and is first immersed to the navel line only, next to the nipple line, then to the prominence of the thyroid cartilage. He gradually accustoms himself to his new surroundings — to the tank and the water. Hearing each time the reading of the amount of water which

9. See table, author's observations.

each section of the body displaces, by the time the last dip is made, the immersion of the head, all fear and trepidation vanishes. In fact, all my subjects showed a lively interest in the experiment and were rather eager to take the last step in the experiment to find out what a "big head" they had. Especially interesting and amusing were the experiments with the boys, which were conducted in groups of two and three. They showed no less interest in the experiment than the observer himself. Only one little boy of 8 could not hold his breath long enough to permit the reading of the water level, but the little fellow made half a dozen attempts and was in tears when he did not succeed. Some of the readings are not recorded on our table because they were not correctly taken, or were not taken at all.

As all my predecessors<sup>3</sup> found the average specific gravity of the human body either too low (Robertson 0.8706, Suelzer 0.970, Herman 0.920) or too high (Krause 1.055, Ziegelroth 1.055, Miess 1.012, Meeh 1.012) as compared with the average specific gravity in our experiments (1.005), I consider it my duty to defend my results on the ground of their greater accuracy.

My tank has a smaller diameter than any of the vessels hitherto used, and because of the smaller diameter the errors in the volumetric measurements were necessarily smaller. Take, for instance, the tank of Robertson, whose dimensions were 183 cm. long and 76 cm. wide. An error in 1 cm. either way would make a difference in the result  $(183) \times (76)$  of 13,908 c.c., a quantity equal in many subjects to the displacement of the volume of one-fourth of the whole body. In my tank (diameter 64 cm.) an error of 1 cm. would make a difference in the result  $(32 \times 32 \times 3.14)$  of only 3,240 c.c., or one-fourth compared with the same error in Robertson's tank.

My observations have demonstrated beyond any doubt that in order to reduce the errors to a minimum, the tank must be made of the smallest possible diameter compatible with carrying out the experiment. The smaller the tank the smaller the error.

#### THE PONDERAL INDEX

One of the properties of living bodies is that of attaining a determinate development, whose limits, in regard to both the quantity of its mass and the harmony of its form, are defined by that biologic final cause which is implanted in the race and transmitted by heredity. These determinate limits constitute a fundamental biological property. One of its descriptive attributes are the limits to be ascertained by measure, namely, the mass of the body, and together with its mass, its anthropologic entirety.

The following measurements have been adopted by modern anthropometrists to determine the form: (1) the total stature; (2) the sitting stature; (3) the total spread of the arms; (4) the circumference of the thorax, and (5) the weight.

Of these measurements stature and weight are the most important. Without them we cannot get the true idea of the form of an individual. For instance, if two individuals have the same weight, 65 kg., for example, and one of them has a stature of 1.85 meters and the other 1.55 meters, it is evident that the first of these two will be very thin, because his weight is insufficient, while the second, on the contrary, will have an excessive weight. A stout, robust child will weigh less in an absolute sense, than an adult man who is extremely thin and emaciated; but relatively to the mass of his body, he will weigh more.

But here a difficulty arises. The linear measurements such as the stature cannot be compared with volumetric measurements such as the weight. It was Galton<sup>3</sup> who ingeniously cut the Gordian knot. He reduced the volumetric measure — the weight — to a linear measure by extracting the cube root from the number representing the weight. Then the root of the weight may be compared to the stature reduced to a scale of 100. This relative ratio between weight and stature is called the *ponderal index*. The formula may be represented as follows:

$$\frac{H}{W} : \sqrt[3]{W} :: 100 : X \quad (\text{where } H \text{ represents the height, } W \text{ the weight, } X \text{ the ponderal index});$$

Hence

$$\text{Ponderal index} = \frac{100 \sqrt[3]{W}}{H}$$

This formula represents an index which is serviceable for practical purposes in the absence of a better one. But since the body does not consist of a homogeneous material I contend that the weight represents the sum of parts differing one from another, the difference in this instance being the specific gravity. For it makes a great difference whether a large proportion of the weight is adipose tissue, brain, or striped muscle. Each of the organs has its special specific gravity. It is evident, therefore, that neither the total weight of the body nor its stature, either separately or relatively, gives us an idea of its volume, less so of its constituent parts.

Let us take the case of two men weighing the same, say 64 kg., and measuring the same length, 150 cm. Both will have as a matter of

course the same ponderal index ( $Pi = \frac{\sqrt[3]{64}}{150} - 20.6$ ),<sup>10</sup> and yet their forms

<sup>10</sup> Livi's Tables of Ponderal Index in Montessori's Anthropology.

may differ, because one is thin and makes up the weight in muscle, and the other is stout and makes up the weight in fat. The cubic root 4 of the weight 64 is after all an empirical number. On the contrary, by taking the weight of the human body in the air and then measuring the amount of water which the body displaces, we obtain two exact measurements, that of weight and that of volume, the ratio of which — the specific gravity — represents the natural and the only ponderal index of the human body.

I recognize the fact that with our present insufficient knowledge of the relative weight and specific gravity of each of the component parts of the human body, we cannot as yet construct a formula which, like that of Archimedes, would give us the respective quantities of the human alloy. And yet I believe that the time is dawning when the anatomists and the pathologists will pay more attention to the weight and specific gravity of every tissue and organ of the human body, and out of the thousands of observations certain definite laws will be deduced which will make it possible to tell from the weight, volume and stature the exact proportion of the weight of at least the three component parts, the musculature, fat and bone, just as it is possible to tell the weight of each component of an alloy if its total weight and the specific gravity of each component part is known.

It is evident that the factor of stature is of equal importance with weight and volume, and therefore the ponderal index which I advocate, namely, the specific gravity, must be based on the three measurements.

The following formula for a new ponderal index, which shall include the trinity of anthropometric measurements—weight, volume and stature, has been suggested by a friend:

Let  $P$  = ponderal index,  $W$  = weight,  $w$  = weight per unit volume,  $V$  = volume,  $H$  = height. Then, according to Galton's formula  $P = \frac{100 \sqrt[3]{W}}{H}$ ; but since  $W = Vw$ ,  $P = \frac{100 \sqrt[3]{Vw}}{H}$ . But  $w = Sw_0$ , where  $S$  = specific gravity and  $w_0$  the weight per unit volume of standard substance (water), whence  $P = \frac{100 \sqrt[3]{VS w_0}}{H}$ . At  $4^\circ \text{ C.}$ ,  $w_0 = 0.9987$  grams per cubic centimeter, in other words  $w_0$  is practically 1 gram, whence  $P = \frac{\sqrt[3]{VS}}{H}$ .

#### THE SPECIFIC EQUIVALENT GRAVITY

We have referred elsewhere to difficulty experienced by various observers in having their subjects dip their heads under water with the normal amount of air in their lungs.

Wengler<sup>11</sup> endeavored to obviate this difficulty by having the immersed person breathe normally while under water through a mask,

11. Virchow's Arch. f. path. anat., 1896, cxlvi, p. 456.

having an outlet from nose and mouth into the air. Meeh<sup>12</sup> thought he could obviate this difficulty by measuring the quantity of air inspired and expired by means of the spirometer, and then adding the result. Both procedures increase the technical difficulties. Jamin and Mueller<sup>13</sup> have therefore devised a method of procedure for the estimation of the specific gravity of the body which is free from the objections above referred to, which consists in taking the specific gravity of the body without obliging the person to dip his head under the water. Their procedure is as follows: The person to be measured is seated in the tank, the surface of the water being at the chin anteriorly and at the border of the hair-growth posteriorly. If we divide the weight of the body by the volume of water displaced when the body is in this position, Jamin and Mueller claim that the quotient, which practically differs from the specific gravity of the body, yet relatively furnishes a constant which gives the relation of weight to volume. The volume of the body, excluding the head, they named the *equivalent volume*. The quotient of the weight of the body and of the equivalent volume they call the *specific equivalent gravity*.

I have already stated that by following my method of gradual immersion beginning first with the umbilical line, then the nipple line, etc., I did not find any difficulty in having the subjects dip their heads while their lungs were filled with the normal quantity of air. I have adopted the specific equivalent gravity of Jamin and Mueller for the reason that the measurements of any part of the body will give constants and after the number of observations has multiplied will give, to use Davy's expression, "information curious and useful." I have indicated in the table the specific equivalent gravity in all experiments.

#### SUMMARY

1. Next in importance to the weighing of the body in the air comes the measuring of the body in water. The first gives us the idea of the mass and the second of the volume. One is not complete without the other.

2. The smaller the diameter of the apparatus the more accurate will be the results. The future apparatus must have the smallest diameter compatible with carrying out the measurement of the volume of the body.

12. Meeh: Ztschr. f. Biol., 1879, xv, 425.

13. München. med. Wchnschr., 1903, i, 1454.

3. It is possible to measure the volume of separate sections of the body.

4. Our conception of the ponderal index must be changed. It should consist primarily of the ratio of weight to volume and refer secondarily to stature

5. The further study of the subject of specific gravity will reveal many new and valuable facts which will have a practical bearing on biology, anthropometry and metabolism.

6. I venture to prophesy that the armamentarium of the future physician will include next to the scales, a specific gravity apparatus.

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## BOOK REVIEW

**CHEMICAL PATHOLOGY.** Being a Discussion of General Pathology from the Standpoint of the Chemical Processes Involved. By H. Gideon Wells, Ph.D., M.D., Professor of Pathology in the University of Chicago and in Rush Medical College, Chicago. Second Edition, thoroughly revised. Cloth, pp. 616. Price \$3.25 net. Philadelphia and London: W. B. Saunders Company, 1914.

A comparison of the second edition of Dr. Wells' chemical pathology with the first edition, published seven years before, gives interesting evidence of the lines along which the chemical study of disease has progressed and an equally striking demonstration of the scantiness of our knowledge of the exact chemical nature of the complex substances concerned in the production of disease and in the organism's defense against it. Dr. Wells does not confine himself to a statement of actual chemical knowledge of pathological lesions and processes in the strict sense, but gives a short survey of the chemistry and physics of the cell, of the nature and action of enzymes and anti-enzymes, and of bacteria and animal parasites and the poisons produced by them, as well as the poisons manufactured by the higher animal organisms.

In these earlier chapters one notes as new especially the discussion of the doubly refractive lipoids and the myelins of the cell, the recent acquisitions in knowledge of anti-enzymes, including Abderhalden's theories, and studies of catalase and anticatalase. There is much new material on autolysis and a very interesting discussion of the correlation of histological and chemical changes in autolysis.

The chapters dealing with the chemistry of the immunity reactions, while excellent short presentations of present knowledge and theories, show most clearly how little these essentially chemical phenomena have been reduced to chemical terms. For the most part these chapters might have appeared equally well in a book on immunity or general pathology, not written from the chemical point of view. The substances involved are still almost wholly hypothetical and of unknown chemical constitution. Vaughan's protein split products approach nearest to definite chemical entities. Friedberger's so-called anaphylatoxin and Abderhalden's *Abwehrfermente* receive consideration. These chapters are placed in a new position in the book and are brought wholly up to date. The discussion of the body's chemical defense against non-protein poisons shows a comparatively small advance in knowledge.

Then follow chapters dealing with the various pathological processes. That on inflammation is to a small extent chemical. In the discussion of circulatory disturbances and diseases of the blood the chief addition to chemical knowledge has been the study of the H-ion concentration by Rolly's gas chain method and Henderson's simpler ones. The most recent theories of fibrin formation, including Howell's, are discussed, but here again, as in the immunity reactions, real chemical substances have not been isolated.

In the chapter on edema the recent studies of colloid chemistry, including Fischer's theory, receive consideration. Of the actual composition of edematous fluids, however, nothing more seems to be known. The nature of the retrogressive pathological changes has received much more satisfactory chemical elucidation, and the discussion of the relation of the lipoids to fatty metamorphosis shows that real progress has been made. For the clinician a fuller presentation of the work on cholesterol in the blood and tissues would have been desirable. The exact chemical nature of amyloid appears as much of a riddle as ever.

The chapter on calcification, concretions and incrustations has been largely rewritten, and as this is a field in which Dr. Wells has himself made large contributions, the discussion is especially excellent.

Little new has been added to the knowledge of pathological pigments, except in the case of ochronosis and the iron pigments.

In the study of tumors chemists have been especially active, and new knowledge on tumor enzymes, hemolytic substances produced by neoplasms and the immunity reactions of tumors is well given. In their chemical composition the study of the fatty constituents of hypernephromas is the chief advance.

The last four chapters deal with metabolic abnormalities or diseases. Uremia and eclampsia receive considerable attention, and the knowledge derived from the study of the blood during life by clinicians is the main evidence of progress. The actual chemical causes of these intoxications, however, are still undiscovered. Acid intoxication and diabetic coma are well presented. Dr. Wells still holds to beta-oxybutyric acid as the mother substance of the acid bodies, though recognizing from Dakin and Wakeman's work the probability that the conversion of beta-oxybutyric and aceto-acetic acids into one another is reversible. Evidence seems to be accumulating that in all probability aceto-acetic acid is the actual precursor of beta-oxybutyric acid. The chapter as a whole has been rewritten and brought up to date. The newer studies of the inborn errors of metabolism, alkaptonuria and cystinuria, which have been so thoroughly described by Garrod, are well discussed. The so-called gastro-intestinal auto-intoxication receive very sane treatment.

In the domain of the ductless glands the chief contributions to chemical knowledge concern the thyroid, but the clinical work is satisfactorily presented in brief, Cushing's studies of the hypophysis being especially notable. Wells maintains a properly critical attitude toward the different problems presented by the adrenals.

A few additions to the real knowledge of uric acid formation and destruction and of the uric acid content of the circulating blood by Folin's new colorimetric method have made the problem of the causation of gout no more intelligible. The concluding chapter on diabetes by Woodyatt is an illuminating presentation of facts and theories and adds greatly to the value of the book.

One misses any reference to the pathological problems of nutrition. The pathology of growth, of obesity or of the nutritional or deficiency diseases which are at the present time receiving so much study is not mentioned. Vitamins would seem as much entitled to a place in chemical pathology as precipitins or opsonins, and one would hope that in a future edition Dr. Wells might expand the scope of his work to include these fields, in which the chemical study of metabolism is proving especially fruitful. He also fails to include the pathological alterations in the total metabolism as revealed by direct and indirect calorimeter studies of fever. The book is especially strong therefore in the presentation of chemical post-mortem pathology—that is, chemical pathological anatomy—though presenting satisfactorily those portions of the chemical pathology of disease in the living which are considered. It is a most valuable reference book for the clinician or pathologist interested in the chemical study of disease and contains an excellent bibliography.

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## AN INVESTIGATION OF THE POTENCY OF TINCTURE OF ACONITE \*

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The pharmacologic action of aconite indicates that the drug should be of distinct use in the treatment of heart disease. The effect of the active principle of the drug, aconitin, on the mammalian heart was studied by Matthews,<sup>1</sup> who described two stages of aconitin poisoning. During the first stage there was slowing of the heart with weakening of systole. The heart-rate was sometimes reduced one-half or one-third of the original rate with a corresponding lowering of the blood-pressure. These effects seemed to be entirely due to central vagus stimulation, as they disappeared after the administration of atropin or after cutting the vagi. During the second stage tachycardia and arrhythmia appeared, apparently caused by the action of the drug directly on the heart muscle. Matthews considers that the drug might be employed therapeutically in such doses that the effects of the first stage alone are obtained, and advocates its use in cases in which it is desirable to stimulate the cardiac inhibitory center without affecting the heart muscle.

Aconitin as such has not been used extensively for therapeutic purposes, but the tincture of aconite has been employed with the hope of obtaining the effects which Matthews predicted. Its use has not been successful, however, as is shown by the experiences of several observers. Thus Rudolf and Cole<sup>2</sup> report that no changes in the heart-rate in patients with various diseases were observed after the administration of a chemically standardized tincture of aconite in doses advised by the British Pharmacopœia. They conclude that the drug is of no value in the usual therapeutic doses. Price,<sup>3</sup> after using aconite obtained

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\* From the Hospital of the Rockefeller Institute for Medical Research.

1. Matthews: A Study of the Action of Aconitin on the Mammalian Heart and Circulation, *Jour. Exper. Med.*, 1897, ii, 593.

2. Rudolf and Cole: The Effects of Medicinal Doses of Aconite upon the Pulse-Rate, *Am. Jour. Med. Sc.*, 1912, cxliv, 788.

3. Price: Recent Advances in the Diagnosis, Prognosis and Treatment of Heart Disease: The Polygraph, *Brit. Med. Jour.*, 1913, i, 477.

from various sources in sixteen cases, including five of heart disease, states that it was never found to have any effect as regards slowing the pulse. Piersol<sup>4</sup> reports but slight effect from the administration of from 15 to 25 drops of the tincture of aconite four times a day to a patient with high blood-pressure, and he is led to question the efficiency of the ordinary doses of the preparation.

My experience with the tincture of aconite as a means of lowering the pulse-rate was obtained in an attempt to influence the tachycardia of exophthalmic goiter. A study of this condition was undertaken on the hypothesis that the tachycardia resulted from a lack of balance between the cardiac accelerators and the vagi and that if the so-called vagus tone could be increased, the cardiac rate would diminish. The attempt to increase the vagus action by means of drugs was but part of the study, and evidence of abnormalities in the nervous control of the cardiac rate was obtained. These, however, will not be discussed at present, as the unexpected results of the administration of aconite prevented the completion of the study.

The tincture of aconite was administered in five cases of exophthalmic goiter, three of which were moderately severe, while two were mild. All of the patients had enlarged thyroids and tremor, while

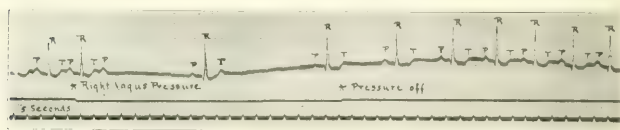


Fig. 1.—Electrocardiogram (Lead 2) showing effect of stimulation of the right vagus nerve by pressure before the administration of the tincture of aconite was begun. Case 2. The R waves in all records have been retouched.

exophthalmos was very marked in two, moderate in two and absent in one case. The pulse-rate after several days' rest in bed ranged from 110 to 120 beats per minute in one case, from 90 to 100 in two, and from 85 to 95 in two cases. In order to ascertain any effect the tincture of aconite might have on the heart in these cases, the pulse-rate was studied under various conditions, both before and during the administration of the drug. These conditions consisted of rest in bed immediately after a constant amount of moderate exercise, and after administration of full doses of atropin. The response of the heart to vagus stimulation by pressure was recorded by means of electrocardiograms, and blood-pressure observations were made daily under as constant

4. Piersol: The Management of High Blood-Pressure, *Therap. Gaz.*, 1913, xxxvii.



conditions as possible. Any symptoms which the drug might cause were watched for.

Besides aconite, the effect of physostigmin in these cases was also studied. Winterberg<sup>5</sup> has shown experimentally that vagus stimulation is more effectual after the administration of this drug, which acts peripherally as regards the vagi, either on the vagus endings or on the heart itself. He suggested that physostigmin might prove useful in cases of tachycardia resulting from lowered vagus tone, and Kaufmann<sup>6</sup> reported favorable results from its use in cases of tachycardia, although it was ineffectual in several cases of exophthalmic goiter. Physostigmin salicylate in a 1 per cent. solution was administered to four of the five patients whom we studied, from 3 to 6 drops three times a day being given. In two cases this drug was given simultaneously with the tincture of aconite. The drug produced indefinite disagreeable sensations with dizziness and faintness before any effect on the cardiac rate was observed, so that its use was discontinued.

The tincture of aconite employed was obtained directly from a firm of manufacturers that has given especial attention to the preparation

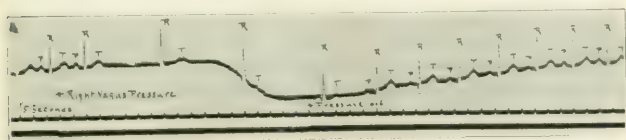


Fig. 2.—The effect of right vagus stimulation when the patient was receiving 7 c.c. tincture of aconite six times a day. Abnormal ventricular complexes are seen during vagus stimulation. Case 2.

of the tincture. The manufacturers cooperated in every way by furnishing the date of chemical assay and all details as to its preparation, as well as suggesting methods of further testing their product. Their assay done shortly before the tincture was obtained showed that it contained 45 mg. aconitin to 100 c.c., thus fulfilling the requirements of the last U. S. Pharmacopeia. The administration to the patients was begun in doses prescribed by the Pharmacopeia, that is, 0.6 c.c. (10 drops) three times a day, 0.27 mg. aconitin being given at each dose. As this dose produced no untoward symptoms and had no effect on the pulse-rate, it was gradually increased until very large doses were administered. The dose in four cases was finally increased to 10 c.c.

5. Winterberg: Ueber die Wirkung des Physostigmin auf das Warmbluterherz, *Ztschr. f. exper. Path. u. Therap.*, 1907, iv, 636.

6. Kaufmann: Physostigmin in Tachycardia, *Wien. klin. Wchnschr.*, 1912, XXXV.

(approximately 150 drops) six times a day, and in one case to 7 c.c. (approximately 105 drops) six times a day. Four patients were thus receiving fifteen times the official dose. Instead of receiving 0.27 mg. aconitin, they were supposed to have received 4.5 mg. per dose or 27 mg. in twenty-four hours. This is thirty times the average dose prescribed by the last U. S. Pharmacopeia, though, as will be seen later, they did not receive quite so large an amount of aconitin. The rate at which the doses were increased varied in the different cases, and the maximal dose was reached in from two to six weeks from the onset of the administration.

The effects of these very large doses will be discussed later, but it suffices here to say that no subjective symptoms were observed, and no slowing of the pulse-rate or lowering of the blood-pressure occurred.

In order to determine the reason why the tincture of aconite did not produce the effects which would be expected from the pharmacologic action of aconitin, the tincture was reassayed chemically and a physiologic assay was done.

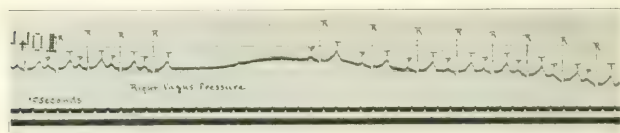


Fig. 3.—The effect of right vagus stimulation eight days after the last dose of tincture of aconite. Abnormal ventricular complexes do not occur. Case 2.

The chemical assay was kindly undertaken by Dr. C. W. Ballard of the College of Pharmacy of the City of New York, Columbia University, to whom I wish to express my gratitude. Dr. Ballard made four assays of the same lot of the tincture which the patients received, using 100 c.c. for each assay. The results indicated by the four assays were as follows:

- Sample "A" contained 0.03648 gm. aconitin per 100 c.c.
- Sample "B" contained 0.03648 gm. aconitin per 100 c.c.
- Sample "C" contained 0.03968 gm. aconitin per 100 c.c.
- Sample "D" contained 0.03776 gm. aconitin per 100 c.c.

The average of the four samples, as indicated by the assay, was 0.03760 gm. aconitin per 100 c.c.

It is thus evident that, on the basis of the U. S. P. method of assay, when the tincture of aconite reached Dr. Ballard's laboratory, it contained approximately 38 mg. aconitin per hundred c.c. or 84.4 per cent. of the aconitin required by the U. S. Pharmacopeia (45 mg.). The lack of activity of the tincture could not, therefore, have been caused by this moderate diminution of the aconitin con-

tent, and the analyses showed that the manufacturers had approximately fulfilled the only standard required by the U. S. Pharmacopeia for the tincture of aconite, namely, the aconitin content as shown by chemical assay.

The physiological assay was carried out by the method described by Roth,<sup>7</sup> and consisted in determining the minimal lethal dose of the tincture of aconite for guinea-pigs. The guinea-pigs were weighed and divided into two parallel series, two animals always receiving the same dose. The tincture was given subcutaneously under the skin of the abdomen in increasing doses and was at first used in a 1:50 dilution. According to Roth, 0.00036 c.c. per gram body weight is the lethal dose of the tincture for guinea-pigs. The first experiment was therefore performed as shown in Protocol 1, a dilution of 1:50 being used:

PROTOCOL 1.—PHYSIOLOGICAL ASSAY OF TINCTURE OF ACONITE,  
EXPERIMENT 1

First Series				Second Series			
No.	Weight gm.	Amount Injected c.c.	C.C. Tincture per gm.	No.	Weight gm.	Amount Injected c.c.	C.C. Tincture per gm.
1	300	2.5	0.00030	1	290	2.5	0.00034
2	320	3.0	0.00037	2	250	2.5	0.00040
3	280	3.5	0.00050	3	250	3.0	0.00048
4	320	4.5	0.00056	4	250	3.5	0.00056
5	300	4.5	0.00060	5	220	3.5	0.00064
6	270	4.6	0.00068	6	220	4.0	0.00073

The guinea-pigs were observed for one hour and then at the end of twelve hours. All survived. The doses administered to the guinea-pigs were gradually increased, the dilution of the tincture being diminished until finally undiluted tincture was employed. It was found that although the drug was at times fatal, guinea-pigs often survived as much of the tincture of aconite as could be conveniently introduced under the skin of the abdomen. This is shown by Protocol 2.

PROTOCOL 2.—PHYSIOLOGICAL ASSAY OF TINCTURE OF ACONITE,  
EXPERIMENT 2

First Series				Result
No.	Weight gm.	Amount Injected, c.c.	C.C. Tincture per gm.	
1	300	1.2	0.004	Survived twelve hours
2	300	1.8	0.006	Died in six hours
3	300	2.4	0.008	Survived twelve hours
4	300	3.0	0.010	Died in six hours
5	300	3.6	0.012	Survived twelve hours
6	270	3.8	0.014	Died in twelve hours

7. Roth: The Physiological Assay of Aconite, Jour. Am. Pharm. Assn., 1913, ii. 705.

## PROTOCOL 2.—Continued.—Second Series

No.	Weight gm.	Amount Injected, c.c.	C.C. Tincture per gm.	Result
1	350	1.4	0.004	Survived twelve hours
2	350	2.1	0.006	Survived twelve hours
3	320	2.6	0.008	Survived twelve hours
4	280	3.0	0.010 +	Survived twelve hours
5	300	3.6	0.012	Survived twelve hours

Guinea-pigs thus survived 0.012 c.c. of the tincture of aconite per gram body weight. As this tincture contained 0.000376 gm. aconitin per c.c., according to Dr. Ballard's analysis, these guinea-pigs survived 0.0000045 gm. aconitin per gram body weight. None of the guinea-pigs in these experiments had been given injections of the tincture previously.

Crystalline aconitin obtained from the same drug firm was tested by the same method. One-tenth of a gram of aconitin was dissolved in 100 c.c. of 2 per cent. acetic acid and then made up to a 1:100,000 solution with sterile 0.85 per cent. sodium chlorid solution. Protocol 3 demonstrates that the minimal lethal dose of the aconitin is at least 0.0000001 gm. per gram guinea-pig.

PROTOCOL 3.—PHYSIOLOGICAL ASSAY OF TINCTURE OF ACONITE,  
EXPERIMENT 3

## First Series

No.	Weight gm.	Amount Injected, c.c.	Aconitin per gm.	Result
1	220	0.55	0.000,000,025	Survived 12 hours
2	220	1.10	0.000,000,050	Survived 12 hours
3	220	1.65	0.000,000,075	Survived 12 hours
4	200	2.00	0.000,000,100	Died in 35 minutes
5	200	2.50	0.000,000,125	Died in 30 minutes

## Second Series

No.	Weight gm.	Amount Injected, c.c.	Aconitin per gm.	Result
1	200	0.5	0.000,000,025	Survived
2	200	1.0	0.000,000,050	Died in 75 minutes
3	190	1.4	0.000,000,074	Died in 70 minutes
4	180	1.8	0.000,000,100	Died in 5 hours
5	170	2.1	0.000,000,124	Died in 65 minutes

The guinea-pigs had not received previous injections.

It is seen, therefore, that the guinea-pigs survived a dose of tincture of aconite which, if the U. S. P. assay method were to be relied on, would have contained forty-five times the minimal lethal dose of crystalline aconitin.

To determine whether the presence of the alcohol of the tincture could be a factor in diminishing its toxicity by decomposing the aconitin, the following experiment was performed: Into 66 per cent.

alcohol, the percentage contained in the tincture, crystalline aconitin was introduced in the same amount as that found in the tincture administered to the patients. This alcoholic solution of aconitin was allowed to stand several days, when it was found that the toxicity of the aconitin was the same as that in aqueous solutions. The alcohol of the tincture was apparently not, therefore, a factor in diminishing the toxicity of the solution by decomposing the aconitin contained in it.

The experiments show definitely that there was such a marked difference between the toxicity of the substance in the tincture giving the chemical tests for aconitin and of crystalline aconitin that the two substances cannot be considered identical. Guinea-pigs survived at least forty-five times as much of the former as of the latter. In fact, the dose of the tincture of aconite which would invariably prove fatal was not determined. It is therefore evident that the surprisingly large doses of the tincture of aconite produced no symptoms in patients because it did not contain a substance with the activity of crystalline aconitin, although the chemical assay as required by the

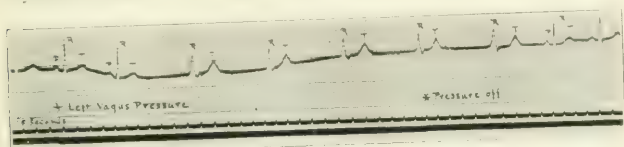


Fig. 4.—Electrocardiogram (Lead 2) showing the effect of stimulation of the left vagus nerve by pressure when the patient had received 10 c.c. tincture of aconite six times a day for five days. Abnormal ventricular complexes during vagus stimulation. Case 3.

U. S. Pharmacopeia indicated that such a substance was present. The cause of this inactivity of the tincture of aconite is not explained.

These facts are brought forward to emphasize the necessity of physiological assays of all drugs which can be so standardized, and also to point out the importance of determining the quality of drugs used before conclusions are drawn as to their effects or the absence of effects. The importance of the so-called "bio-assay" has been pointed out by Wood,<sup>8</sup> who states that the Pharmacopeia requires physiologic standardization of only fifteen drugs out of fifty-three in which such a standardization is possible.

It was previously stated that the large doses of the tincture of aconite produced no subjective symptoms in the five patients with exophthalmic goiter to whom they were administered, and that no

8. Wood: The Purpose and Limitations of Bio-Assay, Jour. Am. Med. Assn., 1912, lix, 1433

slowing of the pulse-rate or lowering of the blood-pressure occurred. In four of the five cases, however, there was observed an abnormal response of the heart to vagus stimulation when the patients were receiving the largest doses of the tincture. Electrocardiograms taken during stimulation by pressure over the left or the right vagus before the drug was administered showed, in all cases, stoppage of the whole heart, except that occasionally with left vagus pressure, waves of auricular activity appeared independently (Fig. 1). When these procedures were repeated during the administration of maximal doses, the electrocardiograms show that in four cases the response to vagus stimulation had changed. Instead of the absence of waves of ventricular activity during vagus stimulation, there appeared ventricular waves of abnormal form, indicating that ectopic ventricular contractions (extrasystoles) occurred during quiescence of the auricles (Figs. 2 and 4). This abnormal response to vagus stimulation disappeared in all the cases when the drug was stopped (Figs. 3 and 5). It is evident, therefore, that the large doses of the tincture of aconite had an effect on the heart, rendering the ventricles more ready to

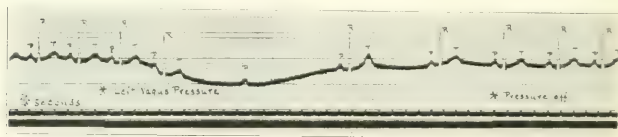


Fig. 5.—The effect of left vagus stimulation four days after the last dose of tincture of aconite. Abnormal ventricular complexes do not occur. Case 3.

contract spontaneously. In other words, the drug apparently increased the irritability of the ventricles.

This effect of the tincture of aconite on the human heart, apparent only during vagus stimulation, resembles the second stage of aconitin action described by Matthews. Similar effects of aconitin on the mammalian heart have been described by Cushny,<sup>9</sup> who found that under the effect of the drug, normally inactive points in the heart take on the power of originating stimuli, the irritability of each part of the heart being augmented.

#### SUMMARY

During a study of the tachycardia of exophthalmic goiter, it was found that very large doses of the tincture of aconite produced no subjective symptoms and no slowing of the heart rate. Doses of 10 c.c. (approximately 150 drops) were given six times a day. An attempt to augment the action of aconite by physostigmin was not successful.



Although the chemical assay showed that the tincture used did not fulfil the Pharmacopeial requirements as regards its aconitin content, the discrepancy was not sufficient to account for the impotency of the drug. The physiologic assay showed that the minimal lethal dose for guinea-pigs of a substance giving the chemical tests for aconitin contained in the tincture was at least forty-five times as large as that of crystalline aconitin, and that the alcohol of the tincture apparently played no rôle in diminishing the toxicity of the solution by decomposing the aconitin. This substance in the tincture can hardly, therefore, be considered identical with crystalline aconitin. These facts emphasize the necessity of physiological standardization of the tincture of aconite, which is not now required by the Pharmacopeia. Evidence was obtained that the maximal doses of the tincture of aconite rendered the ventricles more liable to spontaneous contractions, apparently increasing their irritability.

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9. Cushny: Irregularities of the Mammalian Heart Observed Under Aconitin and on Electrical Stimulation, *Heart*, 1909, i, 1.

# NUCLEAR DIGESTION AND URIC ACID EXCRETION IN A CASE OF TOTAL OCCLUSION OF THE PANCREATIC DUCT\*

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The digestion of nuclear material and the production of purin bases therefrom has been discussed from three points of view: (1) the morphological destruction of the nucleus; (2) the digestion of the so-called nucleoproteids and nucleins; and (3) the splitting of nucleic acid. The localization of the third stage, namely, nucleic acid digestion, has been unquestionably settled by the demonstration of a nuclease in the erepsin of a dog (Nakayama,<sup>1</sup> 1904) and of its absence from the gastric and pancreatic juices (Levene and Medigreceanu,<sup>2</sup> 1911). Confirmatory evidence is afforded by the work of London and Schittenhelm<sup>3</sup> (1910) who found no difference in the nucleic acid metabolism of a normal dog as compared with animals in which the stomach or the pancreas had been removed, or those with a ligated pancreatic duct.

The morphological destruction of the nucleus has been the subject of much controversy since the statement of Adolf Schmidt<sup>4</sup> (1899) that the presence of undigested nuclei in the muscle fibers found in the feces was an evidence of decreased or absent pancreatic function. On this finding, Schmidt based a clinical test consisting of the feeding of small pellets of muscle tissue enclosed in silk bags. He recovered the tissue from the stool, sectioned, stained and examined it for nuclei. Intact nuclei were considered evidence of pancreatic achylia. Kashiwado<sup>5</sup> (1911) modified this test by using thymus nuclei isolated by gastric digestion and stained with hematoxylin—these nuclei were mixed with lycopodium spores and administered in capsules. Kashiwado found in test-tube experiments that neither gastric juice (dog), extract of duodenal mucosa or duodenal juice would digest the nuclei, whereas pancreatic juice quickly accomplished this result. Strauch<sup>6</sup> (1910), using muscle tissue, confirmed Kashiwado's results with the

\* Submitted for publication Dec. 3, 1914.

<sup>1</sup> From the Medical Clinic of the Johns Hopkins Hospital.

1. Nakayama: *Ztschr. f. physiol. Chem.*, 1896, xli, 348.

2. Levene and Medigreceanu: *Jour. physiol. Chem.*, 1911, ix, 65.

3. London and Schittenhelm: *Ztschr. f. physiol. Chem.*, 1910, lxx, 10.

4. Schmidt: *Deutsch. med. Wehnschr.*, 1899, No. 49, p. 811.

5. Kashiwado: *Deutsch. Arch. f. klin. Med.*, 1911, civ, 584.

6. Strauch: *Deutsch. Arch. f. klin. Med.*, 1910, ci, 128.

exception that juice pressed from the intestinal wall seemed to have a slightly destructive effect on the nuclei, and Fronzig<sup>7</sup> (1913), using the nuclei of frog's blood, held that his results agreed with the fundamental principle of the Schmidt test. There has, however, been a great deal of evidence pointing to an opposing view. Glaessner and Popper<sup>8</sup> (1908) found that easily stainable nuclei persisted after digestion with the juice obtained from a pancreatic fistula in a girl of 17, while Hesse,<sup>9</sup> as a result of test-tube experiments and of the insertion of a muscle cube into the stomach (1910), claims that gastric juice will digest nuclei. Van Westenrijk<sup>10</sup> (1911) says that, in the dog, muscle tissue is digested *en masse* in the gastro-intestinal tract, and he holds that muscle tissue without nuclei is never to be found, no matter how the factors of digestion be varied. The clinical experience of many observers (Leech,<sup>11</sup> Pratt<sup>12</sup> and others) has been that the Schmidt test is in no way a dependable one, but the author of the test still (July, 1914) considers it of great value.

It was formerly held that the so-called nucleoproteid was a distinct entity, and several observers (Popoff,<sup>13</sup> 1894; Milroy,<sup>14</sup> 1896) demonstrated to their satisfaction that this hypothetical substance was not split by gastric digestion, whereas it was by pancreatic. Even in the 1914 edition of his *Lehrbuch der Physiologischen Chemie*, Abderhalden assumes two stages of nucleoproteid digestion: first, the formation of "nuclein" from nucleoproteid, accomplished by the stomach, and, secondly, the splitting of "nuclein" into nucleic acid and protein by the activity of the pancreatic juice. This theory of two distinct combinations of nucleic acid with protein has been quite definitely disproved by the work of Umber<sup>15</sup> (1901), who showed that any nucleoproteid is easily split by pepsin or trypsin with the liberation of nucleic acid. Further proof is given by Walter Jones,<sup>16</sup> who demonstrated that the combination of nucleic acid with a protein is merely that of a weak base and a weak acid and is easily reproduced in the test-tube.

When a patient on the medical service of the Johns Hopkins Hospital (whose history is reported below) was found to have a complete absence of pancreatic secretion in the intestinal tract, the idea was conceived that by feeding thymus gland and estimating the increased

7. Fronzig: *Ztschr. f. klin. Med.*, 1913, lxxvii, 84.

8. Glaessner and Popper: *Deutsch. Arch. f. klin. Med.*, 1908, xcix, 46.

9. Hesse: *Ztschr. f. exper. Path. u. Therap.*, 1910, vii, 91.

10. Van Westenrijk: *Ztschr. f. exper. Path. u. Therap.*, 1911, viii, 353.

11. Leech: *Practitioner*, 1911, lxxxvii, 631.

12. Pratt: *Am. Jour. Med. Sc.*, 1912, cxliii, 313.

13. Popoff: *Ztschr. f. physiol. Chem.*, 1894, xviii, 534.

14. Milroy: *Ztschr. f. physiol. Chem.*, 1896, xxii, 307.

15. Umber: *Ztschr. f. klin. Med.*, 1901, xliiii, 282.

16. Jones, Walter: *Nucleic Acids* (Monographs on Biochemistry, 1914).

output of uric acid in the urine, the possible necessity of the pancreas to any stage of nuclear digestion could be conclusively demonstrated. It has long been known that approximately 50 per cent. of ingested purins is excreted in the urine (Weintraud,<sup>17</sup> 1895, and others).

#### CASE REPORT

The patient's history and the clinical findings were as follows:

*History.*—M. W., aged 42 (Med. No. 33,205), a Russian Jew, married, was admitted to the hospital Oct. 20, 1914. The family and personal histories were unimportant. The patient complained of a persistent, painless jaundice (with one slight remission in the first month) lasting for nine months and accompanied by dark urine, rather frequent, soft, clay-colored stools, and 90 pounds loss of weight.

*Examination.*—On examination he was found to be a large-framed man, fairly nourished, but whose skin corroborated the statement of loss of weight. The skin and conjunctivae were intensely jaundiced. The heart and lungs were negative. The liver was large, extending from the sixth rib to the crest of the ilium in the nipple line, smooth, firm and sharp-edged. The gall-bladder was definitely palpated projecting about 2 inches below the liver margin. No other masses were felt; there were no signs of collateral portal circulation. The reflexes were normal. Rectal examination was negative. The temperature, pulse, respiration and blood-pressure were normal.

Blood: White blood-cells, 13,360; polymorphonuclears, 71 per cent.; hemoglobin (Sahli), 83 per cent.; fragility of the red blood-cells, normal; Wassermann reaction, negative; Widal reaction, negative.

Urine: Dark-brown; trace of albumin; few granular casts; bile tests strongly positive.

Stools: Large soft, clay-colored, frequent (while in the hospital the patient averaged three stools daily). Microscopically, marked increase of neutral fats and fatty acids, with the neutral fat clearly predominant; many undigested muscle fibers; hydrobilirubin, negative.

Calmette tuberculin test (1 per cent. and 5 per cent.), negative.

Gastric Analysis: No free HCl; total acidity, 9; no blood or lactic acid; much yeast.

The special pancreatic tests were as follows:

Duodenal contents were obtained with an Einhorn tube and the ferment activities determined by the methods of T. R. Brown.<sup>18</sup>

Trypsin, absent (digestion with 1 per cent. casein solution).

Lipase, absent (digestion with 1 per cent. monobutyryl solution).

Diastase, trace, probably salivary (digestion with one-tenth per cent. soluble starch).

Feces: Brown's<sup>18</sup> technic was used here also.

Trypsin, absent.

Lipase, trace; probably from the lower intestinal tract.

Diastase, absent.

Urine: Diastase, 50 units (high) by Brown's<sup>18</sup> method. Trypsin, absent. Schmidt-Kashiwado nuclei test, negative (spores recovered).

Blood sugar, 100 mg. per 100 c.c. (normal).

Carbohydrate Tolerance: 100 gm. glucose gave no glycosuria.

17. Weintraud: Berl. klin. Wehnschr., 1895, xxxii, 405.

18. Brown, T. R.: Johns Hopkins Hospital Bulletin, 1914, xxv, No. 281.

The patient was discharged Nov. 4, 1914, with the diagnosis of "carcinoma of the head of the pancreas, obstruction of the common bile duct and obstructive cirrhosis of the liver."

The history of nine months of persistent, painless jaundice, associated with a loss of weight, and the clinical findings of a dilated gall-bladder, acholic stools and bile in the urine, point toward a carcinomatous obstruction of the common bile-duct. The inability to demonstrate any of the pancreatic ferments in either the duodenal juice or the feces, coupled with the frequent, large, fatty stools showing many muscle fibers, justifies the assumption that there was a complete absence of the external secretion of the pancreas from the intestinal tract of this patient.

The following experiment was therefore carried out: October 27, the patient was put on a purin-free diet containing 2,900 calories, and the daily uric acid output of the urine determined by means of the Folin-Schaeffer method. On the fifth day (October 31) 150 gm. of fresh calf's thymus were given with the noon meal and the same amount was given on the sixth day (November 1). The purin-free diet was resumed on the succeeding days. The results are found in the accompanying table.

TABLE SHOWING RESULTS OF EXPERIMENT ON A PURIN-FREE DIET			
Date	Diet	Total Urine	Uric Acid
October		c.c.	gm.
27	Purin-free	1,565	0.82
28	Purin-free	1,418	0.76
29	Purin-free	1,420	0.76
30	Purin-free	1,380	0.51
31	Plus 150 gm. of thymus	1,660	1.32
November			
1	Plus 150 gm. of thymus	1,540	1.25
2	Purin-free	1,485	0.15
3	Purin-free	1,279	0.14

The first day's results may be excluded, for a constant level of excretion under the purin-free diet had not been reached at this time. The maximum truly endogenous output was, therefore, 0.76 gm., and the excess of excretion over this amount on the two thymus days was 0.52 gm. and 0.48 gm. By the principle that 50 per cent. of ingested purins is excreted as uric acid in the urine, 150 gm. of calf's thymus should cause an exogenous excretion of approximately 0.6 gm. of uric acid over the endogenous level. It can be safely said, therefore, that there was practically a quantitative recovery of the exogenous uric acid. This finding conclusively demonstrates that there was digestion of thymus nuclei with the production of the uric acid in the urine in the absence of both bile and pancreatic juice.

## SUMMARY

The results of this experiment prove that in the human being the digestion of nuclear material, the purin metabolism and the uric acid formation do not depend on the presence of the pancreatic secretion in the intestinal canal. This finding, together with the negative result of the test in this case, and in many other reported cases, definitely points out the worthlessness of the Schmidt nuclear test for pancreatic function.

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## SECONDARY HYPERTROPHIC OSTEO-ARTHROPATHY AND ITS RELATION TO SIMPLE CLUB-FINGERS \*

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Since the original papers of Bamberger<sup>12, 13</sup> (1889 and 1891) and Marie<sup>113</sup> (1890) numerous reports have been published which have more and more definitely established this morbid condition as a distinct clinical entity among the general group of allied diseases, including leontiasis ossae, osteitis deformans, acromegaly, rickets, syphilis of the bones and others. Walters<sup>210</sup> (1896), Massalongo<sup>117</sup> (1897), Janeway<sup>88</sup> (1903), Thompson<sup>192</sup> (1904), Wynn<sup>218</sup> (1904), Ebstein<sup>48</sup> (1906) and Alexander<sup>1</sup> (1906) have each collected the typical cases from the literature and given a critical review, together with a general discussion of the diseases. In spite of these and many other excellent reports, much regarding the cause, course and real nature of the pathologic changes remains obscure.

The object of the present report is to record the results of the study of five typical cases for a period of years with reference to such considerations as the extent of involvement of the bones and joints, the nature of the process, the course of the disease, and especially the relation of secondary hypertrophic osteo-arthropathy to simple clubbing of the fingers.

### *Group A.—Five Typical Cases of Secondary Hypertrophic Osteo-Arthropathy*

*CASE 1—Acute febrile illness suggesting meningitis followed two years later by hypertrophic osteo-arthropathy; repeated hemoptyses from varix in pharynx; primary new growth of the lungs with metastases in internal organs and right femur; autopsy.*

D. J. R., a man aged 32, entered the Boston City Hospital, March 9, 1909, service Dr. George G. Sears.

*Personal History.*—Until his acute illness three years ago, the patient has always been in perfect general health. Venereal diseases denied. Smoked moderately all his life and as a rule has taken from two to six glasses of beer daily, but very rarely any stronger beverages.

\* Submitted for publication Oct. 3, 1914.

The Roentgen-ray studies were largely made in the Roentgen-ray Department of the Boston City Hospital under the direction of Dr. Francis H. Williams, to whom I am deeply indebted for constant cooperation and advice. My thanks are also due Dr. Walter Dodd of the Massachusetts General Hospital, and Dr. George H. Holmes of the Long Island Hospital, for the examinations made of the cases from those institutions.

The patient's occupation is that of a foundryman and most of the time he works in front of an oven, which work requires him to open the oven frequently, when he is exposed to very intense heat and gases. He is also often obliged to handle the molten metal when it is poured into the mold. At short intervals he goes outside for sand and other materials, and this, during the colder months of the year, necessitates frequent abrupt changes from an excessively hot atmosphere to a very cold one. He states that the vapors from the furnaces not infrequently produce uncomfortable symptoms and at such times he is accustomed to go to the door or window for air. It is not uncommon for workmen in the foundry to be overcome with the heat and gases, especially during the winter months when the ventilation is bad. The victim becomes very pale and usually unconscious, but never exhibits spasms or convulsions. The attacks, as a rule, last but a few minutes, the workman when taken into the fresh air recovering promptly.

About three years ago when on the street, he was suddenly seized with an intense stabbing pain at the base of the skull. By the time he reached home the pain had become agonizing in character and when attempting to untie his shoes, he fell to the floor unconscious. He was confined to bed for three or four months. He states that during most of this period he had a temperature ranging from 101 to 104 F. and much of the time was delirious. The pain which he suffered is described as very intense, constant and boring, confined to a small area in the midline just below the occiput. The head, he said, "felt as though it weighed a ton." The symptoms were somewhat relieved when in a prone position, but on standing or sitting he had the sensation as if the head were resting on sharp spikes, any movement of the head causing it to jostle on these points. There was no retraction of the head, but on account of the pain, motion in the cervical portion of the spine was extremely limited. Many drugs were administered but none gave him the slightest relief from the pain. There were no other special symptoms which he can recall. Convalescence, though protracted, seems to have been complete and after ten months from the onset of the symptoms he went back to his old work where he remained until four months ago. During this period he was in excellent general health and weighed 180 pounds, or more than at any previous time.

During the past four months he has worked in a car barn, being on night duty. His hours were somewhat irregular and his sleep, in consequence, much broken. The building was damp and his work necessitated much exposure during bad weather. He did not feel so well and lost considerably in weight. Up to this time there have never been any respiratory symptoms, the digestion has been good, and the bowels regular.

In spite of his statement that he has been in excellent general health since his recovery from the illness noted above, he gives the history that about a year ago he first experienced pain in the instep which made it very difficult for him to walk about. This symptom was especially noted at night after being on his feet all day. A diagnosis of flat foot was made, but plates gave no relief. Some months later he had pain in the knees also and these joints were very much swollen and tender, but not red. He still remained at work. The joint symptoms have shown a great variation in intensity, but on the whole have become progressively worse. When lying down or sitting comfortably in a chair, there is practically no discomfort, but when walking or standing the joints above mentioned as well as the spine are stiff and motion is painful. After being in a sitting position for some time, he finds it extremely difficult to straighten up and says he feels afraid that the back or knees will give out. He attributes the exacerbations largely to fatigue and changes in the weather. At present the joints are more troublesome than ever. He finds it impossible to keep them in one position for more than fifteen or twenty minutes. He says when moving about he can sometimes feel the fluid shaking in the knees. Of late the hands and wrists have become much swollen. In the case of all the joints the symptoms which were so variable at first have lately become remarkably constant in

character and the pain is much less severe. A symptom which is now much more troublesome than the pain is a sensation as though the skin over nearly all the joints were under great tension. The back is rigid and torsion of the cervical spine, which is limited, causes a creaking sound and a grating sensation.

The patient had never noted any clubbing of the fingers until his attention was called to the condition and he is entirely unconscious of other changes in the arms or legs apart from those described as affecting the joints.

*Physical Examination.* The patient is a well developed but poorly nourished man, slightly pale and very nervous. The degree of emaciation is rather extreme, the *panculus adiposus* having almost entirely disappeared. All the skeletal muscles present a considerable degree of atrophy but this change is most evident in the interossei of the hands. His teeth are neglected, many with cavities. Except for a considerable degree of pallor and excessive perspiration, the



Fig. 1.—(Case 1.) Clubbing of toes and characteristic deformities in joints and lower legs.

skin is normal. The mucous membrane of the throat is slightly pale and shows an atrophic condition. In the inner side of each cheek near the angle of the mouth a few pigmented areas are noted. The lymph-glands are normal. The nipples are enormously increased in size, deeply pigmented and slightly sensitive. The features are unchanged except that the nose is a trifle bulbous.

The appearance of this patient, especially when standing or walking, is very striking, indeed. The trunk is sharply flexed on the thigh and carried very stiffly, the spine seemingly absolutely rigid. The gait is very stiff, clumsy and slow. He gets up and down with the greatest difficulty and finds it almost impossible to climb stairs.

Examination of the spine shows that the normal dorsal and lumbar curves are nearly obliterated and motion in any direction is practically *nil*, except in

the cervical portion, where mobility is still preserved to a moderate degree. Rotation of the head is accompanied by a slight grinding or creaking sound which is readily audible. Any attempt at motion in the dorsal or lumbar spine produces considerable pain. In spite of these changes noted in the spine, no gross changes in the vertebrae are evident. No abnormalities could be made out in the bones of the head. Considering the fact that the patient is a man of large frame, the bones of the shoulder girdle, trunk and pelvis are not considered to be increased in size.

Alteration in the hands, arms, feet and legs are quite extraordinary. Both the hands and feet, but especially the former, are very gross and approach the condition of gigantism. The ends of all the digits are enormously clubbed, the changes involving the whole distal phalanx. The two diameters are almost equal and the clubbed ends are, in consequence, practically globular. Although it is evident that the thickening is largely due to changes in the soft parts, palpation indicates that there is also some bone enlargement. The nails are perhaps a little thickened and the longitudinal ridges augmented, but the most striking change consists in a marked accentuation of the normal curves. The nail-beds are not particularly injected. There is considerable cyanosis. All the joints of the hand are enlarged, slightly tender, and moderately painful with motion, but without any evidence of increase in surface temperature or redness. The changes appear to be largely due to increase in the periarticular soft parts and there is no obvious hydrops articulae. The muscles of the hands, and especially the interossei, are considerably atrophied. Changes of a similar nature but of lesser degree are noted in the joints of the feet. The forearms and wrists are grossly abnormal, the usual tapering form having entirely disappeared. The diameter of the forearm, in other words, appears uniform throughout. The radii and ulnae are clearly enlarged, the surface feeling smooth and regular. There is likewise considerable thickening in the soft parts but no clearly marked edema. The wrists are enormous and present the same appearances as above described in the smaller joints of the hand, except that there is possibly some increase in the joint fluid and the pain with motion is much more marked. The elbow joints also show moderate changes of this same general type. In a general way the changes described in the forearms also pertain to the lower legs, the portions from the knees to the ankles being practically cylindrical. In the lower half, especially, the tibiae and fibulae are easily felt as enormously enlarged throughout. Fairly acute tenderness with firm pressure over the bones. The ankle joints are greatly swollen, apparently contain a considerable amount of fluid and are slightly tender and painful with motion. No other signs of inflammation. Similar changes are present in the knees, but here the bony parts feel very massive. Motion is much restricted.

The lungs, heart and abdominal organs seem normal.

Temperature normal. Examination of the urine gives no evidence of any disease of the genito-urinary tract.

The subsequent history of the patient is interesting, chiefly with reference to the frequent remissions and exacerbations of the disease. In the summer of 1909 the patient was sent to the country for a month's vacation and returned very much improved in general condition and especially with reference to the symptoms in the joints of the legs and arms. The swelling had largely disappeared, the joints were much more supple, there was no longer any pain and only insignificant sensitiveness in the joints with motion. The forearms and lower legs appeared much less massive and even the clubbing in the fingers had slightly diminished. The patient stated that he felt in excellent general condition. Soon after his return he went to work running an elevator and continued at this occupation for nearly three years. During this period he had several sharp exacerbations, with a return of the symptoms in the arms and legs from which he previously suffered. During these exacerbations he suffered also from constitutional symptoms, feeling marked malaise and weakness,

anorexia, insomnia, etc. He was also subject at these periods to excessive sweating, especially at night, and to frequent chills.

In September, 1910, he began to be troubled with a very persistent hacking cough and several times raised blood. When lying on the right side he frequently suffered from a severe choking sensation. At such times he would frequently cough up a considerable amount of fresh blood. The temperature was always found normal. The sputum did not show the presence of tubercle bacilli and no abnormal signs were found in the lungs. Roentgen-ray examination gave no indication of any changes in these organs. A tuberculin test was negative. An examination of the throat by Dr. Leland revealed the presence of an enormous varix behind the epiglottis, which was evidently the source of the hemorrhages. Treatment of this condition gave entire relief from hemorrhages for nearly a year.



Fig. 2.—(Case 2.) Clubbing of fingers and toes. Typical deformities in forearms, lower legs, wrists and ankles.

In the fall of 1912 the patient was finally obliged to give up his work permanently and from that time on the course of the disease was steadily progressive. The symptoms in the legs and arms remained about the same but he became gradually weaker and found it more and more difficult to get about. He was excessively nervous, much depressed and at times showed symptoms of insanity. He frequently showed symptoms of cardiac weakness and examination gave signs of mitral insufficiency and dilatation. He also developed a very extreme and persistent blepharitis.

His condition finally became so critical that in September, 1913, he was again sent to the Boston City Hospital. For the first time definite signs were found in the lungs. There was slight dulness at the right apex, to the spine of the scapula behind and to the third rib in front. Over this area the breathing was

moderately bronchovesicular in type and the fremitus definitely increased. No râles. A Roentgen-ray examination showed a fairly dense shadow corresponding to this area of dullness, but no other changes in the lungs. There were no pulmonary symptoms. A diagnosis of pulmonary tuberculosis was made and the patient referred to the Boston Consumptives' Hospital, where he died Dec. 10, 1913.

*Roentgen-Ray Examination March 11, 1909.*—The entire skeleton was examined at this time and at regular intervals until the patient's death, Dec. 10, 1913. Considering the relatively slow development of bone changes in general, it was thus possible to study the progress of the disease in the osseous system for a period of nearly five years. In the history above, attention was called to the extraordinary exacerbations and remissions which took place from time to time in the clinical course of the disease. Considering its distribution and its severity, it is not surprising that we fail to find any definite evidence of bony absorption: coincident with the periods of remission. Although for considerable periods bony changes seemed to be at a standstill or progressed only slowly, the general course over the period of five years was one of more or less irregular progression and the contrast between the appearances in the bones at the time of the first and last examination is very striking.

March 11, 1909, the Roentgen-ray examination gave the following: Nearly the entire skeleton shows to a greater or lesser degree alterations in the bones characteristic of hypertrophic osteo-arthritis but are most marked, as is usually the case, in the long bones of the forearms and lower legs, the phalanges of the feet and hands, and the carpus and tarsus.

The essential bony changes consist in a subperiosteal formation of new bone, the original osseous tissue appearing normal and the two everywhere distinctly differentiated.

The distal phalanges in both the feet and hands show a general burr-like proliferation in their outer portion. All the bones of the metacarpus and metatarsus show alterations which consist in an even layer of new bone throughout the diaphysis, varying in thickness from one sixteenth to one-eighth of an inch in the case of the first metatarsal bone. In a few instances there is an irregular, cauliflower-like proliferation over the epiphyseal part. Similar changes are also seen in the first row of phalanges in both the hands and feet, but of much less degree than in those just inside. In several at about the level of the outer and middle third, the lateral ridges which form the attachment for the flexor tendons show a relatively immense proliferation. In the middle row of phalanges proliferation is noted only occasionally and the distal phalanges are unchanged except in their outer half.

The tarsus and carpus participate in the changes to a rather slight degree. The os calcis in either foot gives no evidences of abnormalities, except that in the lower half of the posterior portion there is a considerable degree of formation of new bone, continuing down into the tuberosities, which are considerably increased in size. The radii and ulnae of both forearms are immensely altered, the subperiosteal layer of new bone being present throughout their entire length, but thickest about an inch above their distal extremity and gradually diminishing in thickness toward the elbow joint. In the case of both bones, the greatest deposit is on the outer side. In the case of both radii for an extent of about two inches at their distal ends, there is an immense deposit of irregular new bone which extends to the joint line. A similar picture is seen in the bones of the lower legs. A thin shell of new bone is readily made out in the lower third to one-half of the humeri, also in the outer half of the clavicles and the acromion processes. The bones of the head and the ribs seem normal. In contrast to the humeri, the femora are changed throughout their entire length and to a considerably greater degree, but much less, however, than the bones of the lower legs. The patellae are considerably changed in their non-articular portion. Characteristic osseous changes are shown along the crests



of the ilia, but otherwise the pelvis is normal. No definite bony proliferations can be made out in the spine.

The joints are everywhere surprisingly free, there being no evidence of changes in the joint cartilages. In the ankles, knees, wrists, elbows and several of the joints of the hands and feet, the irregular proliferation of bone in the epiphyseal portion of the bones forming the joints stops abruptly at the edge of the cartilage.

Subsequent roentgenograms show the successive stages in the process of bone proliferation just described. In the bones most involved the sharp line of demarcation between the old cortex and the new subperiosteal layer gradually disappears and finally in the bones of the lower legs is almost nowhere to be



Fig. 3.—(Case 37.) Marked clubbing but no enlargement of forearms and lower legs. Roentgen-ray shows slight formation of new bone in the tibiae.

made out. The outline of the long bone is in many places quite smooth and regular, but in others is very much broken and uneven. Small cysts, varying from one-half to one centimeter in length, are in several places to be made out. In contrast to the appearances shown in the early roentgenograms, the later ones show a very great decrease in the density of the original bony shaft. The entire structure is apparently altered, the marrow space is completely obliterated and the normal texture of the bones replaced by a shadow which is very thin and of extremely variable and irregular density, somewhat resembling the appearances seen in advanced osteitis deformans. Even in the roentgenogram taken but a few months before death, the joints are still seen to be free, although the changes immediately adjacent, described above, are greatly augmented.

*Necropsy* No. 170, Dec. 10, 1913, by Dr. J. Earle Ashe.

*Anatomical Diagnosis.*—*Periostitis ossificans; primary carcinoma of the right lung with metastasis in right femur, left kidney, brain, and left lung; chronic adhesive pleuritis; chronic bronchitis; moderate chronic fibrous mitral valvulitis, early coronary sclerosis; spleen, chronic tumor; moderately fatty liver; moderate chronic interstitial nephritis; moderate hydrops and multiple yellow softenings from emboli in the brain; visceroptosis; chronic blepharitis.*

**Body:** Moderately emaciated. Pupils are equal, regular, 5 mm. in diameter. The palpebral conjunctiva is congested, the edges of the lids, especially the lower, are much thickened and excoriated and there is a small amount of thick, yellow, purulent material in the right outer canthus. The ears are rather prominent, the teeth well preserved and the palatal arch rather high. The tongue and jaws show no enlargement. Patches of yellow, superficial, dry, bran-like scales over upper chest and lower abdomen. The breasts are a trifle more prominent than usual. External genitals normal. None of the superficial lymph-nodes are enlarged except the epitrochlear, which are readily palpable. The radial arteries are stiff and tortuous.

There is some irregular thickening of the lower ends of both humeri, though the shafts are apparently free. On the radii and ulnae, however, can be felt distinct irregular thickenings, more marked on the lower ends of the former, though the shafts are distinctly involved. The finger ends are markedly clubbed, apparently due chiefly to enlargement of the soft parts. The nails are of the typical "Uhrglassform" and the free edges are widely separated from the fingers by a thick matrix. They are a little thick, but not hard or dry. No alteration of the carpal or metacarpal bones can be detected. The thighs are partially flexed on the abdomen, the legs likewise on the thighs. In both cases it is impossible to overcome these contractures. The lower ends of the femurs are greatly thickened by irregular bony masses. Just above the inner tuberosity of the right femur is a distinct mass which as felt through the skin is rather soft and contains particles of bone. The right knee joint was exposed and found moist and contained fairly firm black blood clot, slightly adherent to the articular surfaces of the condyles. There are several small superficial erosions of the articular surfaces of the right condyle of the femur, external tuberosity of the tibia and outer facet of the patella. There is a small, fairly sharp exostosis springing from the base of the tibial spine. The tumor felt through the skin is 6 cm. long by 3 cm. wide and 3 cm. in thickness. It is covered by thick periosteum and the outer two-thirds is firmly fibrous and contains cancellated bone. The inner portion is soft, lobate, and of a brownish-red color and the adjacent portion of the shaft under the tumor is eroded to conform to its shape, and so deeply in the lower portion that the inner condyle is practically a shell. About the tumor there is a considerable amount of loosely clotted blood. The tumor does not seem to be attached to the bone except by the periosteum and can be shelled out of its nest in the bone without difficulty, leaving an area of porous exposed bone, which is apparently not infiltrated by the tumor.

The femur was exposed for its lower half. It is enormously thickened—posteriorly by long stalactite-like exostoses—longer and thicker over the tuberosities, and all pointing upward. The remainder of the surface is made up of fairly uniform plaques of subperiosteal bone, which are thicker toward the lower end. The periosteum is somewhat thickened; the new bone is very firm and cannot be separated from the original shaft. The fibulae are both much enlarged, the lower two-thirds being almost as thick as the tibiae. They are rather rough and irregular as palpated through the skin, while the tibiae are comparatively smooth. The left tibia was exposed at about its middle. The periosteum was found moderately thickened, beneath which flat plaques of new dense bone had been laid down. The cortex beneath this is hard, averaging about 1 cm. in thickness. Beneath this again is a thick layer of cancellated bone enclosing yellow, apparently unaltered, marrow.

The right leg from the middle down and including the foot is swollen and pits on pressure, edema being due to pressure on the femoral vein by the tumor in the region of the knee. The skin of the soles of the feet and under surfaces of toes is thick, rough, and of a light brown color. There is distinct clubbing of the toes with bowing of the nails. The second toe of the right foot incised on under surface and enlargement found to be due chiefly to thickening of the soft parts. The distal phalanx was excised and found to be much broader than normal at its tip.

Head: External occipital protuberance is palpable, but not enlarged. The hair is thick. The scalp strips fairly easily. Calvarium is not thickened but the bone is somewhat more dense than usual due to the fact that the diploe are not quite so prominent as usual. Skull averages 0.5 cm. in thickness. The dura is free from the calvarium and from the underlying membranes, except



Fig. 4.—(Case 39.) Marked clubbing, but only suggestive thickening in the lower leg. Roentgen-ray reveals rather general bony proliferation.

along the longitudinal fissure, where Pacchionian bodies penetrate. There is some edema of the subarachnoid space over the upper surfaces of the frontal lobes. The pia and arachnoid are otherwise free. The vessels are well filled, particularly those of the vertex and show no sclerosis. The posterior end of the left internal orbital convolution is adherent to the orbital plate of the frontal bone for an area of 1 cm. in diameter. When these adhesions are broken the cortical tissue immediately beneath is soft and white with small yellow mottled areas. In the posterior portions of the middle frontal convolutions on both sides are areas of similar cortical softening with the yellow mottling. In posterior portions of the upper frontal on the left side is a soft area, but more gray and without the yellow color. These areas are all practically the same

size, i. e., from 1 to 1.5 cm. in diameter. The ventricles and appendyma are free.

The pituitary body is readily removed from its position, measures 14 by 6 mm. and is of usual consistency. On section, however, it is darker than normal, apparently from the presence of blood. There is found to be some exaggeration of the sinus markings in the lower fossa of the skull, particularly the left lateral sinus, which is almost entirely surrounded by bone. The crista galli is much more prominent than usual, extending into the falx for 1.5 cm. and the anterior portion of the occipital bone bulges posteriorly quite perceptibly, though not enough to compromise the medulla. The bony air sinuses are not enlarged and are free from exudate.

On section a number of small areas of cortical softening are disclosed aside from the ones already described.

1. Left middle occipital, 0.5 cm.
2. Posterior tip of hippocampal 1 cm.
3. Left ascending parietal, 0.5 cm.
4. Upper surface, right gyrus fornicatus, about the middle, 1.5 cm.
5. Right lenticular nucleus, about the middle, 1 cm. in diameter running practically the whole length and involving a small portion of middle of internal capsule.
6. Lower end of the ascending frontal and parietal convolutions that cover in the Island of Reil, and extending into the contiguous cortex of the Island, 1.5 cm. in diameter and 2 cm. long.
7. Left marginal convolution, lower edge, 1 cm. in diameter.
8. In tegmentum of the pons.

These foci are all in the state of yellow, or early light softening.

Primary Incision: The primary incision shows nothing remarkable. Costal cartilage, ribs and sternum normal. Thymus practically obliterated. Pericardial sac free.

Left Lung: Pleura at apex slightly thickened and adherent, at which point the parenchyma is thickened also. In lower lobe three small masses 1 to 2 cm. in diameter, circumscribed, hard and cut surface whitish with reddish brown center. Vessels and bronchi free.

Right Lung: Pleura densely adherent over posterior portion of upper and adjacent upper one-quarter of lower lobes. Parenchyma crepitant throughout middle lobe and in anterior half of upper and all but upper portion of lower. The remainder is uniformly infiltrated. On section these infiltrated areas appear grayish-white with small yellow mottling and of firm consistency. This tissue is continuous in the two lobes through the interlobular pleura. The tissue behind this indurated parenchyma is red, necrotic, rather pultaceous, and largely ulcerated away to form a very irregular cavity in both lobes. The walls are granular but show no fibrosis. The overlying pleura is infiltrated but the ribs do not seem to be involved.

Heart: Moderate fibrosis of mitral valves.

Spleen: Enlarged, 320 grams. Capsule smooth and tense; consistency increased.

Stomach, intestines, pancreas and suprarenals appear normal.

Liver: Slightly enlarged and edge rounded. On section the central zones are dark and somewhat depressed, the peripheral areas of the lobules are of a yellowish tint.

Kidneys: Moderate interstitial changes. On the anterior surface toward the upper pole of the left is a slightly elevated white nodule 2 cm. in diameter. On section it is found to be 8 cm. deep and the cut surface is white, with bright yellow mottlings.

*Microscopic Diagnosis.*—Primary carcinoma of lung (right from bronchial mucosa), metastasis to left lung, left kidney, periosteum of right femur, lymph-gland right knee, multiple to brain; ossifying periostitis; chronic splenic tra-



Fig. 5.—Roentgenogram of left hand (Case 1) showing characteristic subperiosteal new bone covering the shaft of the radius and ulnae. Note the erosion of the epiphyses, "beading" of the metacarpals, and one row of subperiosteal irregularities covering the phalanges. Single arthralgia is evident in the distal phalanges.

*beculitis and capsulitis. Heart: Cloudy swelling; focal chronic interstitial myocarditis. Liver: Chronic passive congestion; moderately fatty. Suprarenal: Congestion. Kidney: Moderate chronic interstitial and capsular nephropathy. Pituitary: Hyperplasia. Soft parts of fingers and toes—obstructive distention of sweat ducts; some hyperplasia.*

*Microscopic Examination.*—Brain: Sections from four of the areas of cortical softening show identical features. The center is necrotic and surrounded by tumor cells which in type and arrangement conform closely to those of the parent tumor. Considerable glial hyperplasia in surrounding brain tissue.

Spleen: Capsule, trabeculae and artery walls moderately thickened.

Heart: Some cloudy swelling and focal areas of fibrosis.

Liver: Moderate central congestion and some fatty infiltration in the peripheral cells.

Adrenals: Marked congestion; considerable vacuolization of cortical cells.

Kidney: Changes largely interstitial and of only moderate type. The tumor metastasis consists of dense connective tissue enmeshing adenomatous mass of tumor cells. The renal tissue is invaded.

Pancreas: Slight fatty infiltration.

Pituitary: Moderate increase in number of gland cells with very little hyalin substance in acinar spaces.

Lungs: In the infiltrated areas the alveolar tissue is entirely displaced by the tumor, which consists of columnar epithelium supported by a vascular young connective tissue stroma and forming irregular alveola-like spaces. In some areas these spaces are filled with tumor cells unattached to the lining cells and much more irregular in size and outline, though distinctly epithelial in type. The nuclei vary greatly in size and shape and many show mitotic figures. No cilia are found. A few spaces are lined with young, regular cuboidal cells such as are seen in the fibrosed lungs, and which show only slight evidence of malignant characteristics. In the tumor cells crowded in the spaces there is a tendency to metamorphosis to the squamous type. The tumor is essentially cellular, but in a few small areas the connective tissue stroma is increased and shows hyalin. Several areas of necrosis and some hemorrhage are seen along the edge of the tumor. Rarely there is evidence of slight inflammatory reaction. Sections from various areas of the tumor and the nodule in the left lung present identical characteristics.

Tumor at Right Knee (Fibrous Cortex): Adenomatous groups of cuboidal cells surrounded by abundant young connective tissue. Several areas of necrosis, involving both connective tissue and tumor cells. The inner, softer portion is more cellular, the squamous type predominating and of the general arrangement seen in the primary growth in the lungs.

Lymph-Gland at Knee: Lymph tissue entirely replaced by connective tissue in which are imbedded irregular masses of squamous tumor cells closely packed. Small amount of surrounding hemorrhage.

Finger: From dorsum, at root of nail, rather thick layer of cornified epidermis. Some edema of cutis and arterial walls are thickened.

Eroded bone at site of periosteal metastasis. Very active osteoclastic bone destruction of cancellated tissue, at the same time there is new bone being developed on the trabeculae by osteoblasts. Some hemorrhage into marrow spaces. Small groups of tumor cells, showing acinar arrangement, usually, are in the marrow spaces nearest the surface.

Toe: Soft tissue from ball. Thick layer of cornified epidermis. Papillary layer markedly indented. The striking feature is the dilatation of the sweat-ducts. They are tortuous and can be followed into epidermis where an occasional cross section shows lumen occluded by hyalin material.

Terminal Phalanx of Toe: Loose cancellated bone, with distinct hypertrophy of sides, where narrow spaces are filled with loose, young connective



tissue containing stellate cells and a thick layer of elongated cells (osteoblasts) are laid down on the bone trabeculae.

Femur: New subperiosteal bone, much looser than normal cortical bone. Osteoplastic bone formation is still going on. No osteoclasts. Most of the marrow spaces contain fat and the usual marrow cells. Others are plugged with small particles of disarranged bone trabeculae enmeshed in a mass of partially necrotic cellulo-fibrillar material.

Tibia: Subperiosteal new bone, cross section. Wide Haversian spaces contain fat and marrow cells in some instances, in others a loose young connective tissue containing stellate cells. On longitudinal section the subperiosteal line is rather irregular from active lacunar resorption. Masses of osteoblasts on under surface of periosteum particularly over points of osteoclastic activity. Some of the marrow spaces contain necrotic bone as described in other section. Medulla not remarkable.



Fig. 6.—Roentgenogram of right leg (Case 1). In the femur the layer of new bone is sharply marked off from the old shaft which remains essentially unchanged. The epiphysis is free. The tibia and fibula are altered throughout and retain very little of the normal Roentgen-ray appearance. The line of demarcation between the old and new bone is not present. Both bones show uniform alterations in the epiphysis as well as the diaphysis, but the knee joint is only slightly involved. The patella is correspondingly altered.

Marrow (Tibia): Rather richly vascular fatty tissue containing a few spicules of bone and very few cells, the latter about the blood vessels. These cells are mostly mononuclear though there are a few polynuclear cells and several megalokaryocytes.

CASE 2—*Pleurisy with effusion; chronic pulmonary tuberculosis with extensive cavity formations; tuberculous enteritis; mitral regurgitation and stenosis; pulmonary hypertrophic osteo-arthropathy.*

E. M., aged 30, entered the Boston Consumptives' Hospital July 10, 1908.

*Personal History.*—Until the onset of the present illness the patient enjoyed excellent general health. Venereal diseases denied. Habits good except for excessive cigarette smoking.

About four years before entrance he had a severe attack of pleurisy with effusion and was tapped. The convalescence was very slow and he has never regained his former good health. He was examined at that time at the Boston Dispensary and no signs of pulmonary tuberculosis were found. About a year later he had another severe attack of pleurisy and a diagnosis of pulmonary tuberculosis was then made. He was sent to the State Sanatorium at Rutland, Mass., where he remained for about six months, improving greatly in general health.

Since the first attack of pleurisy, he has had nearly constant cough, which has become increasingly severe in character, and has lost much in strength and weight. The sputum, which was at first scanty, has become more and more purulent, at times has contained blood and is frequently very foul. There is severe dyspnea with exertion. About three years ago he was troubled for some time with severe night-sweats, but since then has had none. There have been no gastric or urinary symptoms, no edema.

The patient noted at the time of the first attack of pleurisy that the ends of the fingers were slightly larger than normal and he is positive that he has observed a gradual increase in this condition from year to year. He is quite as positive that there were never any changes in the forearms or lower legs until within the last six months, since which time there has been a definite increase in the size. No pains whatsoever are experienced in either the forearms or lower legs, but the bones are exceedingly sensitive to pressure and if injured slightly are sore for some days.

*Physical Examination.*—The patient presents a typical picture of advanced consumption. He is excessively weak, dyspneic with the slightest exertion, coughs frequently and raises an abundant, rather foul, greenish-yellow sputum.

The heart presents the classical signs of mitral regurgitation. There is an extensive bilateral process in the lungs, with signs of softening which are more marked on the right (tuberculosis).

Abdominal examination negative. Reflexes normal.

The arms distal to the elbow joints and the legs below the knee joints present a most striking condition. The forearms look massive and the normal proportions are very much altered, the forearm above the wrist being much enlarged so that it seems almost cylindrical, the lower portion being hardly less in diameter than the upper. There seems to be no definite edema but the soft parts feel thickened. More particularly, the bones are felt to be distinctly enlarged, the surface smooth and tender to deep pressure. The hands appear in general rather massive, but without edema. The most striking thing is the rather extraordinary clubbing of the ends of all the fingers, the thumb showing the most exaggerated form. The nails are much thickened and show an accentuation of both curves—the "parrot-beak" type. Moderate cyanosis of the nails. The nail bed is raised and definitely hyperemic. The wrists and ankles are greatly swollen and stiff and motion is moderately painful, yet there is no redness or increase in the surface temperature. The knees are less affected. The lower legs and feet present changes exactly analogous to those described in the hands and forearms though perhaps slightly more marked. Clubbing in the great toes is distinctly more than in any others.

Sputum greenish-yellow, mucopurulent, moderately fetid in odor. Large number of bacteria with many typical tubercle bacilli, single and in clumps. Urine examination negative.

The patient remained in the hospital until April 22, 1909, and improved very satisfactorily in general condition although the process was not considered arrested. At this time he left against advice to go back to work. Since then he has been frequently readmitted but on the whole has steadily lost ground.

April 24, 1910. Patient's general condition is distinctly worse than at entrance in 1908. The process in the lungs has advanced strikingly. The left lung shows marked signs throughout and evidences of a large cavity in the

midscapular region behind and from the second to fifth rib in front. The heart is displaced to the left to such a degree that the right border is about 2 cm. to the left of the left sternal border.

The condition in the limbs described above is more striking than ever.



Fig. 7.—Roentgenogram of right ankle (Case 1) taken March 11, 1909. Note the sheath of new bone surrounding the lower end of the tibia as far as the epiphysis, the fibula throughout, the shaft of the metatarsals and the proliferation along the outer edge of the os calcis and the cortex of the bones.

Roentgenograms of the entire skeleton made at this time show the following: The phalanges of the left hand present no abnormalities, unless it be a slight proliferation in a few of the distal ones. All the metacarpal bones, however, show a distinct thin layer outside the shaft, involving the bone throughout its entire length. The deformity is greatest in the metacarpal bones of

the thumb and little finger. The process seems to be confined entirely to the shaft of the bone in each case. There are no definite changes in the carpus, but the lines between the individual bones are more or less obliterated. The joints throughout the hand are normal. The left radius and ulna present changes exactly similar to those described in the metacarpal bones except that the outer layer of the new bone is more irregular and variable in density. There is no change to be noted in the ends of the bones and the joints are free. In the right hand as in the left, the phalangeal bones are normal. All the metacarpal bones with the exception of the third have a definite thin layer outside the old shaft, which is most marked in the thumb and first finger. Changes of the same type and degree as in the left are noted in the right ulna and radius. The arteries do not show.

Roentgenograms of the upper arm and shoulder girdle are without evident changes in the bones. A few of the ribs, however, show a questionable deposit of subperiosteal new bone. The bones of the skull and face are normal.

The phalanges of the feet are normal, but the first, fourth, and fifth metatarsal bones show slight but definite changes of exactly the same type as noted in the metacarpal bones. The tarsus is free from changes. The tibia and fibula in both legs show an irregular, definite layer of subperiosteal bone throughout the shaft, in places nearly a quarter of an inch in thickness. These changes in places extend beyond the epiphysis nearly to the joint surface in the case of the knees. The femurs present alterations noted in the bones of the lower legs but of much less extent. Nothing definitely abnormal can be made out in the pelvis.

A year later a second series of roentgenograms was made of the entire skeleton. During the interim the patient's condition had remained about the same. The alterations from the normal in the bones as shown by the roentgenograms are similar to those described, but are considerably more marked in all the bones previously involved and several of the phalanges of the hands and feet show beginning changes. The distal phalanges in the feet are particularly noteworthy as they have increased considerably in size, showing irregular osteophytic outgrowths mainly in the outer half but also to some extent just distal to the joints.

In April, 1911, the patient was discharged from the hospital and was not readmitted until March 24, 1913, when he seemed to be in a dying condition. The general symptoms referable to the process in the lungs were much more severe, the sputum of a definitely putrid type and very abundant in amount. There was marked cyanosis, dyspnea and considerable edema of the lower legs. He was also suffering from a violent diarrhea with five to ten loose movements daily and considerable colicky pain.

After a few weeks' residence in the hospital, he began slowly to improve, which improvement continued and by March 12, 1914, when a third set of roentgenograms was made, the patient had made extraordinary improvement. He had gained enormously in weight, was up and about the grounds daily, and suffered from almost no symptoms except dyspnea with any unusual exertion. He had practically no cough, raised no sputum except a small amount in the morning. Pulse and temperature were normal. The signs in the lungs, however, did not differ materially from those previously found, except that they were much less definite of activity.

The roentgenograms are in striking contrast to those made a year and two years previously. The bones of the hand show no changes whatsoever, except that the terminal phalanges are slightly ragged and possibly a little enlarged, and several of the bones of the metacarpus seem a little massive and dense, but without any clearly defined cortical layer of new bone. The appearances in the bones of the forearms are essentially the same as previously but a little less marked and the differentiation between the old shaft and the new bone less definite; that is, to a considerable degree the new bone seems to have



Fig. 8—Roentgenogram of right ankle (Case 1) taken June 25, 1913. Changes in the bone as evident in Fig. 7, but of more striking degree, are present, and also in the old bone throughout.

become fused with the old. The thickness ranges from one-eighth to one-quarter of an inch. The outline is somewhat irregular.

The terminal phalanges of the feet are but little if any broader and more ragged than normal. Nothing abnormal except questionable changes in a few of the metatarsal bones. The roentgenograms of the lower legs present the same general type of changes as described earlier, but there has evidently been a great retrogression in the process previously described as having taken place in the bone.

*CASE 3.—Syphilis at 36; chronic alcoholism; cirrhosis of the liver; chronic pulmonary tuberculosis, with cavity; pulmonary hypertrophic osteo-arthritis of acute febrile type.*

T. F. D., aged 54, entered the Boston Consumptives' Hospital Dec. 2, 1909.

*Personal History.*—In early years had measles, scarlet fever and pertussis. Typhoid fever in 1889. Seventeen years ago a severe attack of influenza. For many years a very hard drinker and a man of generally dissolute habits. Gonorrhea fifteen times and on several occasions chancroids and buboes. Eighteen years ago he had a chancre followed by secondary eruption which was untreated, but since then he has had no further symptoms of syphilis. April 27, 1905, he entered the Massachusetts General Hospital for severe hematemesis. His condition at that time was diagnosed as cirrhosis of the liver and chronic alcoholism. Somewhat later he developed paralysis of the vocal cords together with some symptoms of pressure in the mediastinum and a roentgenogram showed a slight dilatation of the arch of the aorta. In September, 1909, he again entered the hospital with an infected tarsal cyst. Following operation he had an open wound for a long period, with considerable discharge of pus. This wound was not finally healed until a secondary operation was done nearly a year later.

November 12, 1909, the patient entered the Boston City Hospital with pulmonary symptoms and there a diagnosis of pulmonary tuberculosis was made. Tubercle bacilli were found in the sputum in large numbers.

At entrance to the Boston Consumptives' Hospital the patient gave a history of a hemorrhage from the lungs about seven years previously. Since this time he has had a nearly constant cough, as a rule loose in character, but with a variable amount of sputum. For a considerable period he had had severe gastric symptoms and marked dyspnea with exertion. There has been considerable loss of strength and a decrease in weight from 185 pounds six years previously to 150. No fever, chills or night-sweats.

*Physical Examination.*—This is negative except for signs of a fibroid phthisis involving nearly the whole of the right lung and the left above the third rib, and a much enlarged liver with hard, irregular edge.

The fingers and toes show a moderate clubbing of the characteristic type, but no abnormal signs in the long bones are made out. Temperature 98 F., pulse 70, respirations 20. Urine negative. Sputum shows the presence of many tubercle bacilli.

About a month after entrance the patient began to complain of pain and stiffness of the lower spine. Shortly afterwards the left knee and leg became swollen, also both forearms, wrists and hands. The signs in the lower legs and arms, however, were not so much in the region of the joints as in the long bones. The chief symptom was a dull, constant pain which was described as deep in the bones. The forearms and lower legs were clearly enlarged, not reddened but with excessive tenderness over the bones, which felt definitely increased in size. The ankles, knees, wrists and some of the finger joints were enlarged and slightly stiff but without signs of inflammation. In spite of rest in bed and careful treatment the condition of the patient remained unchanged for several weeks, when very slow improvement took place. After several months, however, the forearms and lower legs looked less massive but the bones still felt larger than normal. This improvement in the acute condition in the



forearms, hands, feet and legs described above followed a marked improvement in the pulmonary condition. The pulmonary symptoms practically all disappeared, the temperature came down to normal and the physical signs in the lungs decreased strikingly in intensity and extent.

Unfortunately it was not possible to examine the patient with the Roentgen ray until May 7, 1910, at which time he was ready to be discharged from the hospital as an arrested case. He had gained about 50 pounds in weight and all symptoms, both of the disease in the lungs and in the limbs had entirely disappeared. The signs in the lungs had diminished materially. He had a slight dulness at both apices with bronchovesicular respiration, moderate increase in fremitus and a few scattered râles. Over a small area in the right front at the level of the second rib, distinct amphoric breathing, with slight egophony, were heard.

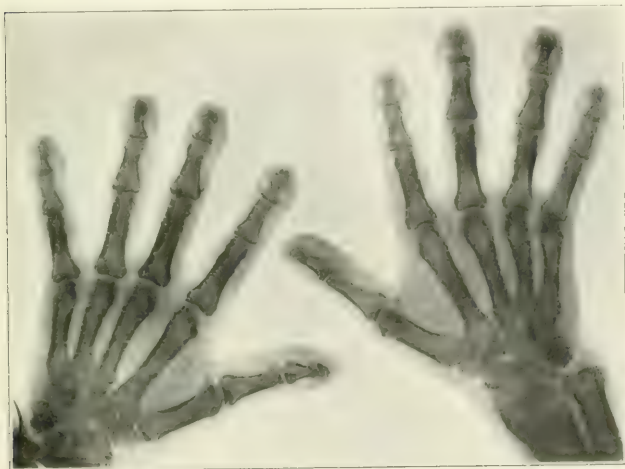


Fig. 9.—Roentgenogram of hands (Case 4), designed to illustrate the type of proliferation in the distal portion of the ungual phalanges seen in hyperostrophic osteo-arthritis. The remaining bones show only slight indications of the peripheral new bone present some years previously.

Forearms and lower legs still appeared more cylindrical and slightly larger than normal, but otherwise nothing abnormal could be made out. The clubbing of the fingers, though less, was still rather marked. Only slight cyanosis of the nails.

*Roentgen-Ray Examination.*—The terminal phalanges of the hands show marked but variable enlargements, the outlines being ragged and irregular. Many of the remaining phalanges seem to be thickened in the cortical portion of the shaft and the outline in places is ragged, but the line between the outer sheath of new bone and the old shaft is not everywhere evident. The bones of the feet show less marked changes. The bones of the forearms and lower legs are thickened but do not show anywhere a well marked layer of new bone. The cortex is much thicker than normal, slightly irregular in outline, and in many places gives the impression definitely of the fusion to a greater or less

degree of newly formed subperiosteal bone with the old cortex as seen in other cases. The arteries of the legs and forearms are clearly seen as tortuous, calcified lines. There is a definite though thin layer of new bone along the lower edge of the ilia and to some degree in the upper half of the femurs.

The appearances about many of the joints are noteworthy. All of the distal joints of the fingers show a greater or lesser degree of proliferation of bone, in some instances of definite osteophytes, mostly at the proximal end of the last phalanges. The ends of the next rows of phalanges forming the joint are much misshapen and irregular but without osteophytes. In several cases the line representing the joint cartilage is much thinned and the general appearance is that seen in osteo-arthritis. The middle phalangeal joint and the metacarpal-phalangeal joint appear normal. The carpus is greatly changed. In certain places actual proliferation of the bone can be seen, but the most striking thing is the appearance of matting together of nearly all the bones. The radio-carpal joints seem free. Both elbow joints, but the left more than the right, show considerable change which consists chiefly in considerable proliferation in the olecranon process and an indeliteness in the joint line, evidently the result of bony proliferation. Changes of the same nature, as above described in the fingers, are seen in the toes, being most marked in the distal joints, but present also in the middle phalangeal joints. Lateral roentgenograms of the ankle joints show general changes in all the bones of the tarsus. There is a more or less constant layer of new bone which stops abruptly at the joint surface. No lipping can be made out. In both knees over the outer side of the external condyle of the femur and of the upper end of the tibia the surface is much roughened and proliferated with small osteophytes, especially on the tibia.

During the next year the patient continued free from symptoms and the signs in the lungs diminished. The appearances in the limbs remained about the same. Roentgenograms made March 28, 1911, showed the same general appearances as described above, but slightly less clearly defined.

*CASE 4.—Pneumonia; empyema; bronchiectasis; pulmonary hypertrophic osteo-arthritis.*

M. M., a foundryman, aged 43, entered the Boston City Hospital May 9, 1903.

*Personal History.*—Patient has always been rugged until the past two years. He smokes and drinks to excess but denies venereal diseases.

Two years ago he had severe pneumonia, with good convalescence and apparent cure, followed about five months ago by a second attack from which he has never fully recovered. Since then he has had almost constant, increasingly severe cough, often paroxysmal, with large amounts of greenish-white foul sputum; soreness in the left side of the chest with catchy pain on coughing; dyspnea; frequent headaches and anorexia; considerable nausea and vomiting; in a word, greatly impaired general health. No chills or night sweats.

The patient is entirely unconscious of any changes in the bones and declares that he has had no symptoms there.

*Physical Examination.*—A powerfully built, robust man whose general appearance gives the impression of a severe acute illness. He is somewhat pale; there is considerable cyanosis, and dyspnea is marked even when making the slightest exertion.

There are unmistakable signs of fluid in the left chest. The heart is considerably displaced to the right but is otherwise normal. The peripheral arteries are soft and not tortuous. Pulse 110, temperature 102 F., weight 170 pounds.

The sputum is mucopurulent in character and does not show the presence of tubercle bacilli. The urine is normal.

The forearms, lower legs, feet and hands present a typical condition of hypertrophic osteo-arthritis. The hands appear gross and clumsy, although there is no edema. The terminal digits are almost globular, diameters being

nearly equal and the nails showing an extraordinary degree of curving, with great thickening and the presence in all of prominent longitudinal ridges. The forearms and lower legs are much enlarged, giving a rather cylindrical appearance but without any tenderness over the bones, or edema. The joints nowhere show any evidence of involvement except for moderate swelling, motion being perfectly free and without pain.

Soon after the above date the patient was operated on for empyema and a large accumulation of pus found. The patient was considerably relieved as a result of the operation, but even after several months, when the wound was healed, he still suffered from almost constant cough and with frequent evacuation of a large amount of sputum of the same type as described above. He improved considerably in general health, gained in weight (204 pounds), was much less short of breath, and finally resumed his work. He was seen, however, from time to time in the out-patient department and usually had a slight rise of temperature, varying from 99.5 to 101 F. The signs in the lungs remained essentially the same.



Fig. 10.—Roentgenograms of forearms (Case 40) showing a thin, irregular layer of newly formed bone about the lower diaphyses of the ulnae and radii.

May 6, 1914. During the past ten years the patient has been under my personal observation and at periods of six months to a year roentgenograms have been made to show changes if any taking place in the bones. He has worked constantly and improved steadily in general health. The weight has held steadily at 205 to 210 pounds. Except for the cough and dyspnea with exertion he feels that he has never been so well. The cough, though less severe than in former years, is still harassing. It is worse at night and in the early morning after rising. The sputum is small in amount, never purulent or of foul odor. The forearms are frequently painful, though never tender. Dull pains are also present about the knees at times.

On examination signs are still present in the left lower back, but of much less definite character than previously. There is still some cyanosis of the lips. In general the changes in the limbs appear to have subsided to a considerable degree.

The Roentgen-ray examination revealed much more extensive alterations in the skeleton than were evident on physical examination. The characteristic bone changes seen in hypertrophic osteo-arthritis are present in the bones of the forearms, lower legs, lower third of humeri, and in the lower third of the femurs. The bones of the feet are more altered than are those of the hands. The distal phalanges are strikingly fan-shaped, very irregular and at their proximal ends near the joint surface nearly all show a few small osteophytic growths. The second row of phalanges are but little changed, whereas the first and the metatarsal bones all show more or less subperiosteal proliferation of bone. The changes in the hand are of a similar nature, but less marked. The remaining bones of the skeleton appear unchanged.

The changes in the joints are rather striking, especially the knees, ankles, elbows and wrists. In each instance besides the evident thickening in the soft parts, there is marked proliferation of the bone immediately adjacent to the joint surface and especially in the knee there is marked lippling. In these joints the cartilage is quite irregular and in a few places almost obliterated. In the case of the elbow joints, the increase in the bone substance is certainly much greater in the ulna than in the humerus, the olecranon process being greatly augmented in size by irregular newly-formed bone throughout the greater sigmoid cavity. In the carpus on each side there is a slight appearance of matting together of certain of the bones and in a few, slight proliferation is to be made out. About the epiphyseal portion of the radius and the very border of the joint cartilage is an immense, irregular, cauliflower-like new bone formation. The joint cartilage is evidently normal. In the hands and feet, only the most distal joints are essentially altered. The principal change consists in the proliferation of adjacent parts as in the case of the large joints, but in the feet the joint cartilage also seems more or less changed.

The roentgenograms made in subsequent years show the same general changes. There is no evidence that the process has advanced and indeed in many of the bones there has been a more or less striking retrogression. The layer of subperiosteal new bone has become thinner, somewhat more dense in places, and, as a rule, less sharply marked off from the original shaft.

CASE 5.—*Pleurisy with effusion; old phthisis; asthma; arteriosclerosis; pulmonary hypertrophic osteo-arthritis.*

Mrs. C. C., aged 48, Boston City Hospital, Out-Patient Department, No. 16320. Seen Dec. 6, 1907.

*Personal History.*—Usually in excellent general health. About twenty years ago, the patient had an attack of pleurisy in the right side, followed by a dry, hacking cough for some months. Occasional attacks of asthma since childhood, which later diminished in severity and none now except very rarely in the cold weather. Pneumonia seventeen years ago.

Since last March she has had gradually increasing dyspnea, no palpitation, slight edema of the ankles and burning, toothache-like, intermittent pains in the long bones which are worse at night, when she is fatigued, and in cold and wet weather. At first they were chiefly in the legs, lower back, and forearms, but are now confined to the upper third of the left arm and along the course of the spine between the shoulders; occasionally in the wrists and knees, with some tenderness over the site of the pains. She has noticed for the last few months increasing stiffness and clubbed deformity of the ends of the fingers, which occasionally feel cold, but never numb, and with no other disturbances of sensation. The patient has lost 25 pounds in weight during the past year.

The general health is good, but she finds that she is weak, clumsy and slow in getting about.

*Physical Examination.*—A very tall, emaciated, sallow looking woman. Skin atrophic. Lips and fingers cyanotic. The face appears gross and somewhat mask-like, somewhat suggestive of acromegaly. Pupils react normally. No glandular enlargement.

Chest: Left clavicle more prominent than right; right side of chest seems to move less with respiration than left. Apical outline on right considerably diminished, and whole right side dull, becoming flat below the third rib front and a point two inches above the inferior angle of the scapula behind. In the upper part of the right chest the respiration is faint and of vesicular character; over the lower part, practically absent. Fremitus is normal above, but absent over lower part of right chest.

Heart: Normal in position. Left border just outside left nipple line. Impulse felt in sixth space. Sounds clear, rather sharp. No murmurs heard. Aortic second sounds somewhat accentuated. Pulse regular, rather full volume and high tension. Arteries tortuous and palpable.

Abdomen negative.

The bones of the lower legs and forearms in their lower third feel slightly enlarged and the parts appear definitely massive. No tenderness. Slight edema of the ankles. Knees somewhat swollen, evident thickening of the soft parts, and bony structures also feel massive; signs of small amount of fluid; motion normal; no redness or tenderness. Fingers and toes clubbed and of characteristic type.

No tubercle bacilli found in the sputum. Temperature 99.4 F. Urine normal.

*Roentgen-Ray Examination.*—All the distal phalanges of the hands and feet are more or less changed, in some instances rather strikingly. Several of the first row of phalanges show slight characteristic changes. In the metatarsus and metacarpus all the bones show a varying degree of subperiosteal formation of new bone. All the bones of the forearms and lower legs show changes practically throughout the shafts, the layer of new bone varying from one-sixteenth to one-quarter of an inch in thickness and being most pronounced at the distal ends. The outline is fairly even. The lower femur is slightly changed. No other bones of the skeleton are found changed.

The only joints showing any changes are the knees. Here the periarticular soft parts are evidently thickened. There is considerable proliferation of the epiphyseal portion of the bones forming the joint, the irregular new bone extending to the cartilage border and in a few places there is actual lipping, as in osteo-arthritis. The interarticular cartilages are a trifle more irregular than normal.

The patient was admitted to the wards Jan. 8, 1908, where she remained until Jan. 16, 1908. While in the hospital paracentesis of the chest was done and 16 ounces of clear, serous fluid withdrawn.

Soon after discharge the patient went to her home in Nova Scotia and nothing is known of her condition since.

#### DISCUSSION

No summary of the recorded cases of secondary hypertrophic osteoarthropathy has been made since 1906 when Alexander<sup>3</sup> published a synopsis of seventy-seven typical cases. As this author has apparently overlooked a few genuine cases of this disease, and as a considerable number have been published since the appearance of his paper, I have for purposes of discussion later, attempted an analysis of all the examples in medical literature with reference to the primary disease. As the description in many instances is extremely meager and no post mortem or Roentgen-ray examination is recorded, the selection of typical cases must be a somewhat arbitrary one. In the following col-

lection I have included only those in which the clinical picture was absolutely typical, or in which a post mortem or Roentgen-ray examination showed the presence of lesions in the bone characteristic of this disease.\*

#### JANEWAY'S CASES

CASE 1.—Male, aged 35; nine months' history of cough with evidence of chronic empyema communicating with a bronchus eight months after onset of primary lesion, pains in ends of the long bones coincident with enlargement of hands. Extreme clubbing of finger-ends; cyanosis and definite bone enlargements of wrists and fingers.

CASE 2.—Male, aged 34; indefinite history; aortic endocarditis, irregular fever and chills accompanied by severe pains in ankles, knees and wrists. Swelling of extremities, followed three or four months later by extreme clubbing of the fingers (toes less); marked enlargement and some tenderness of the lower ends of the long bones. There was no fluid in the knee joints and the fingers were not cyanotic. Primary lesion probably a *Streptococcus viridans* endocarditis.

CASE 3.—Male, aged 29; history of appendicitis four years before; pain in the right chest for five months; dyspnea, loss of weight, enlargement of extremities for few weeks and pain in wrist and ankles. Signs of fluid at right base; enlarged liver; secondary anemia. Distinct clubbing of the fingers, without cyanosis, and enlargement of the bones, both wrist and ankle. Radiographs by Dr. Cole showed definite though not extensive bone changes of osteo-arthritis. Five weeks after he was first seen he coughed up blood and chocolate-brown pus, characteristic of a liver abscess, and a month later the enlargement of the wrists and fingers diminished. Complete recovery, and four years later in perfect health, when Roentgen ray showed that the enlargement of the soft parts had greatly diminished and that there was no change in contour or structure of the bones of the hand or arm.

\* The following cases (Abadie,<sup>1</sup> Armour,<sup>2</sup> Bailly,<sup>8</sup> Bécélère,<sup>11</sup> Bernhardt,<sup>10</sup> Chatin and Cade,<sup>33</sup> 2; Chauffard,<sup>34</sup> Combemale and Chatelin,<sup>37</sup> Combemale and Sonnevillle,<sup>35</sup> Emerson,<sup>51</sup> Fischer,<sup>35</sup> Flückiger,<sup>56</sup> Gibson,<sup>68</sup> Gilbert and Fournier,<sup>60</sup> Gilbert and Lereboullet,<sup>70</sup> Gillett,<sup>71</sup> Godlee,<sup>73</sup> 3; Goulesbrough,<sup>74</sup> 5; Gries,<sup>76</sup> Groedel,<sup>77</sup> Hartung,<sup>82</sup> 2; Hillier, unpublished, Hirschfeld,<sup>84</sup> 3; Hoffmann,<sup>90</sup> Jamet,<sup>87</sup> Joffroy,<sup>69</sup> Jovane,<sup>91</sup> 3; León y Avelés,<sup>104</sup> 4; Macewen,<sup>107</sup> Maeshima,<sup>108</sup> 5; Marfan,<sup>112</sup> 3; Marie,<sup>114</sup> Marina,<sup>119</sup> 2; Miller,<sup>123</sup> Möbius,<sup>124</sup> Moizard,<sup>125</sup> 2; Moussous,<sup>127</sup> Murray,<sup>129</sup> O'Carrol,<sup>132</sup> Orillard,<sup>134</sup> Parmentier and Castaigne,<sup>138</sup> Pidcock, unpublished, Puyhaubert,<sup>144</sup> Reed,<sup>140</sup> Reynaud and Audibert,<sup>153</sup> 5; Rotch and Dunn,<sup>155</sup> Ruehle,<sup>157</sup> Saundby,<sup>161</sup> Schmidt,<sup>163</sup> Schou,<sup>164</sup> Sevestre,<sup>165</sup> Smirnov,<sup>168</sup> Taylor,<sup>183</sup> 784 Thompson,<sup>186</sup> Thorburn,<sup>193</sup> Variot and Chicotet,<sup>199</sup> Vas,<sup>202</sup> Vedel,<sup>206</sup> Villard,<sup>208</sup> West,<sup>214</sup> 2, although in many instances included by one or more of the previous writers as cases of hypertrophic osteo-arthritis, I have excluded since the clinical report, while giving evidence of clubbing of the fingers and toes, makes no mention of the characteristic changes in the long bones. Many are probably true examples of this condition, but the description is so incomplete as to make them of no value. Twenty-two other cases which are mentioned in the literature of hypertrophic osteo-arthritis (Chrysospathes,<sup>30</sup> Elliott,<sup>50</sup> Field,<sup>54</sup> Fraentzel,<sup>55</sup> Friedrich<sup>62</sup> and Erb,<sup>62</sup> 2; Gasne,<sup>63</sup> Gerhardt,<sup>61</sup> Gessler,<sup>67</sup> Guérin and Etienne,<sup>75</sup> Hirtz,<sup>80</sup> Jolly,<sup>69</sup> Koll,<sup>84</sup> Legrain,<sup>100</sup> Méry and Guillemot,<sup>110</sup> Postmantir,<sup>142</sup> Sollier,<sup>170</sup> Spieler,<sup>172</sup> Tournier,<sup>105</sup> Verstraeten,<sup>200</sup> v. Recklinghausen,<sup>147</sup> Virchow,<sup>207</sup>), I have excluded as being examples of other conditions than the one under consideration. In only a few is there evidence even of true clubbing of the fingers. The papers by Fragle<sup>59</sup> and Mestre<sup>120</sup> I have not been able to obtain.



TABLE 1.—PUBLISHED CASES GROUPED ACCORDING TO THE PRIMARY DISEASE

## A. DISEASES RESPIRATORY TRACT

Abscess of lung.....	1	Kerr. <sup>92</sup>
Bronchiectasis .....	27	Alexander, <sup>3</sup> 4; Bamberger, <sup>13</sup> 6; Botez, <sup>24</sup> Brooks, <sup>23</sup> 2; Dennig, <sup>25</sup> Doeblin, <sup>46</sup> 2; Emerson, <sup>51</sup> Freytag, <sup>61</sup> Godlee, <sup>73</sup> Jane- way, <sup>63</sup> Maguire, <sup>109</sup> Massalongo, <sup>117</sup> Mosti, <sup>129</sup> Sitta, <sup>107</sup> Thompson, <sup>122</sup> Wynn, <sup>218</sup> 2.
with emphysema .....	2	Brooks, <sup>29</sup> Gillett. <sup>71</sup>
with empyema .....	2	Godlee, <sup>73</sup> Thayer. <sup>182</sup>
with infantilism and lymphatism	1	Franchini. <sup>60</sup>
with meningitis .....	1	Brooks, <sup>23</sup>
with pleurisy .....	1	Thayer. <sup>182</sup>
with pulmonary tuberculosis.....	3	Bamberger, <sup>13</sup> Emerson, <sup>51</sup> Janeway. <sup>88</sup>
with pulmonary tuberculosis and spinal caries .....	1	Walters. <sup>211</sup>
with chronic nephritis .....	1	Brooks. <sup>29</sup>
with syphilis .....	1	Van Deventer. <sup>107</sup>
Bronchitis .....	5	Blakeney, <sup>22</sup> Brooks, <sup>29</sup> Edgar, <sup>49</sup> Genova, <sup>44</sup> Stockman. <sup>190</sup>
with emphysema .....	1	Thirolloix and Jacob. <sup>189</sup>
with emphysema and syphilis....	1	Reynaud and Audibert. <sup>153</sup>
with pleurisy .....	2	Emerson, <sup>51</sup> Pichard, <sup>120</sup>
with pneumonia .....	2	Stembo, <sup>175</sup> Roubinovitch. <sup>156</sup>
with pneumonia and cardiac dila- tation .....	1	Brooks. <sup>29</sup>
with pulmonary tuberculosis.....	1	Salles and Halipré. <sup>120</sup>
Cyst of lung (hydatid).....	1	Thoinot and Delambre. <sup>190</sup>
Empyema .....	8	Bondi, <sup>23</sup> Genova, <sup>94</sup> Janeway,* Lefeb- vre, <sup>90</sup> Raugier, <sup>146</sup> Rendu and Boul- loche, <sup>151</sup> Thayer, <sup>180</sup> 2.
with bronchiectasis .....	1	Démons and Binuad. <sup>44</sup>
with bronchitis .....	2	Davis, <sup>42</sup> Mouisset et Orsat. <sup>128</sup>
with chronic nephritis .....	1	Emerson. <sup>51</sup>
with adhesive pericarditis .....	1	Springthorpe. <sup>174</sup>
with pneumonia .....	1	Thompson. <sup>101</sup>
with pulmonary tuberculosis.....	1	Prokop a Stretti. <sup>143</sup>
Influenza .....	1	Redmond. <sup>145</sup>
Malignant disease—		
Cancer lung .....	1	Thompson. <sup>192</sup>
Cancer mediastinum .....	1	Strangeways and Ponder. <sup>181</sup>
Cancer mediastinum, lungs and pleura: endocarditis .....	1	Ewald. <sup>53</sup>
Lymphadenoma of mediastinum.	1	Weber. <sup>212</sup>
Sarcoma of lungs .....	4	Alexander, <sup>3</sup> Cagnetto, <sup>32</sup> Hall, <sup>79</sup> Saundby. <sup>160</sup>
Sarcoma of mediastinum .....	1	Hasbrouck. <sup>83</sup>
Pleuritis, effusion .....	1	Sternberg. <sup>178</sup>
Pneumonia .....	1	Barot and Pichard. <sup>15</sup>
with bronchitis .....	1	Brooks. <sup>29</sup>
with endocarditis, chronic neph- ritis .....	1	Schittenhelm. <sup>162</sup>
Streptothrix of lungs .....	1	Landis. <sup>98</sup>
Pulmonary tuberculosis .....	16	Brooks, <sup>23</sup> Curl, <sup>40</sup> Harris, <sup>81</sup> Landis, <sup>88</sup> Lockwood, <sup>105</sup> Maguire, <sup>109</sup> Massalongo and Gasperini, <sup>118</sup> Mestre, <sup>120</sup> Métin and Guillion, <sup>121</sup> Mettenheimer, <sup>122</sup> Spill- mann and Haushalter, <sup>173</sup> Steven, <sup>179</sup> Teleky, <sup>185</sup> Thérèse, <sup>187</sup> Thompson, <sup>188</sup> Thorburn. <sup>193</sup>

TABLE 1.—(Continued.)

Pulmonary tuberculosis—		
with aortic insufficiency.....	1	Bamberger. <sup>13</sup>
with empyema .....	2	Gouraud <sup>15</sup> and Marie, <sup>113</sup> Packard. <sup>187</sup>
with pleurisy with effusion;		
aortic stenosis .....	1	Waldo. <sup>200</sup>
with spinal caries .....	2	Thorburn. <sup>103 194</sup> Whitman. <sup>216</sup>
with stenosis of esophagus.....	1	Hartung. <sup>152</sup>
	<hr/>	
	108	

## B. DISEASES CIRCULATORY TRACT

Aortic insufficiency .....	1	Bamberger. <sup>13</sup>
Congenital heart—		
Defect of septum.....	1	Shaw and Cooper. <sup>188</sup>
Pulmonary stenosis.....	1	Bamberger. <sup>13</sup>
Endocarditis .....	1	Janeway.*
Mitral stenosis; hydatid cyst of		
liver .....	1	Thorburn. <sup>103</sup>
Pulmonary stenosis; aortic insuf-		
ficiency .....	1	Bamberger. <sup>13</sup>
	<hr/>	
	6	

## C. DISEASES ALIMENTARY TRACT

Abscess of liver .....	1	Janeway.*
Abscess of liver, empyema and		
syphilis .....	1	Reed. <sup>140</sup>
Hypertrophic biliary cirrhosis.....	6	Gilbert et Fournier. <sup>10</sup> 2; Obermayer, <sup>131</sup>
		3; Van den Bergh. <sup>106</sup>
Chronic enteritis .....	2	Renner, <sup>152</sup> Telkey. <sup>153</sup>
Chronic jaundice .....	3	Obermayer, <sup>131</sup> 2; Décloux and Lipp-
		mann. <sup>45</sup>
	<hr/>	
	13	

## D. MISCELLANEOUS

Abscess of axilla, syphilis, pulmon-		
ary tuberculosis .....	1	Newton and Mercelis. <sup>180</sup>
Abscess salivary gland.....	1	Wolfsohn. <sup>217</sup>
Cancer of breast, neck, larynx,		
thyroid .....	1	Kruger. <sup>95</sup>
Polyuria .....	1	Apert and Rouillard. <sup>4</sup>
Spinal caries; amyloid disease.....	1	Thompson. <sup>102</sup>
Syphilis (congenital), jaundice.....	1	Thompson. <sup>102</sup>
Syphilis; pelvic abscess; pulmon-		
ary tuberculosis with cavity.....	1	Chrétien. <sup>35</sup>
	<hr/>	
	7	
No known antecedent disease.....	5	Gluzinski, <sup>72</sup> Reed, <sup>140</sup> Soltan, <sup>171</sup> Symons, <sup>383</sup>
		van der Weijde en Buringh Boek-
		houdt. <sup>108</sup>

\* Through the courtesy of Dr. Janeway I am able to give a summary of three of his unpublished cases.

Hypertrophic osteo-arthritis is so generally secondary to some obvious primary disease that the occasional recorded instances which are apparently without relation to some antecedent disease are worthy of careful consideration as particularly affecting the question of etiology. In all, twenty-one such examples are quoted in the literature. Case 1 of this report must also be discussed with this group.

Gerhardt's<sup>66</sup> case, although accepted by Wynn<sup>218</sup> and Janeway<sup>88</sup> as a true case of hypertrophic osteo-arthritis, seems to me from the description given to be more characteristic of acromegaly, as an example of which it was published. The case of Gessler<sup>67</sup> likewise should be classified as probable acromegaly. Postmantir's<sup>144</sup> case is doubtful, although the fingers are mentioned as clubbed. Guérin and Etienne<sup>78</sup> conclude that their case is not a true example of Marie's type. Schmidt<sup>103</sup> published a very meager history of a woman of 48 with hypertrophy of the ends of the fingers and toes, but without mention of bone changes, in which the only antecedent diseases were rheumatism and acquired syphilis twenty-three years previously. Improvement with potassium iodid is recorded. The case does not appear typical and, indeed, one is left with the impression that the condition is probably entirely due to the luetic infection. These five cases then can be eliminated without further discussion as atypical or doubtful.

The remaining sixteen cases are all probably examples of osteo-arthritis, although in several instances the history is somewhat meager. In three of them (Apert and Rouillard,<sup>4</sup> Gouraud<sup>75</sup>-Marie,<sup>113</sup> Lockwood<sup>106</sup>) a definite disease is mentioned which seems clearly to have been the primary condition, and these should consequently be excluded. In eight others the past history is so suggestive of a primary basis for the osteo-arthritic changes that they cannot be accepted as unquestioned examples of primary osteo-arthritis. Brooks,<sup>29</sup> in commenting on his own case (No. 5), states that, while no pulmonary lesions can be demonstrated, the history of many previous attacks of bronchitis makes it quite probable that it is one of pulmonary origin. Wolfsohn's<sup>217</sup> patient, a man of 34, had an operation for inflammation of the salivary gland at 24, soon after which he first observed the changes in the fingers. The author expresses the opinion that the osteo-arthritis may have been secondary to this inflammatory process. He acquired syphilis two years after the diagnosis of osteo-arthritis was evident. In one (Décloux and Lippmann<sup>43</sup>) there is an indefinite previous history of icterus, erysipelas of both lower legs and synovitis. In the case of Newton and Mercelis,<sup>130</sup> a man of 33, there was a family history of tuberculosis with a personal history of a morning cough for years. He was rejected four times for the army because of "weak chest." Twelve years previously he had an ulcer on

the penis, presumably the primary lesion of lues. At the time of the observation he entered the hospital for a large axillary abscess, which, after operation, ran a very protracted course. Salles and Halipré's<sup>150</sup> case had a family history of tuberculosis and he had had, five years previous to the first observation, a severe and obstinate bronchitis. There were also indefinite signs in the lungs at the time the condition in the bones and joints was described. Spillmann and Haushalter<sup>173</sup> state that in their case the signs of the disease appeared a year previous to the development of pulmonary tuberculosis. In view of the fact that pulmonary tuberculosis is frequently of very insidious type and may exist for many years before being recognized, it would seem probable that an unrecognized tuberculosis of the lungs was the focus. Similarly in Steven's<sup>170</sup> case there is evidence of a more or less chronic process in the lungs with cough, but at the time of entrance to the hospital no signs of disease were found in the chest. Thiroloix and Jacob<sup>189</sup> publish their case as one of the primary type and the lungs as normal, but in the history state that he was a chronic sufferer from tracheobronchial catarrh and emphysema. While it is impossible in the above eight cases to state precisely the primary disease, the presence of some condition known to cause changes characteristic of osteoarthropathy is so strongly suggested by the history in each that it seems fair to challenge them as primary cases.

There remain then but five cases which offer any definite positive evidences of the existence of a primary type of hypertrophic osteoarthropathy (Gluzinski,<sup>72</sup> Reed<sup>149</sup> (Case 4), Soltau,<sup>171</sup> Symons,<sup>182</sup> Van der Weijde en Buringh Boekhoudt<sup>198</sup>). Each author particularly states that there was no antecedent disease and the histories are uniformly without definite suggestion of such, although in several the clinical description is meager. In Soltau's case the patient gave a history of a severe attack of influenza eighteen months previously, but no signs or symptoms of any pulmonary disease remained. These cases lose much of their significance, due to the fact that in none was a post mortem examination made, without which it is impossible to state positively that no primary disease was present. Mention is made of a Wassermann reaction in only two and a tuberculin test in only one. It is very reasonable, then, to consider that some cardiac or pulmonary condition, some obscure focus of infection or a liver cirrhosis, might have existed without being manifest.

Furthermore, it may be possible that in rare instances osteoarthropathic changes may, when once well established in the tissues, and contrary to the usual course of the disease, become progressive in spite of healing of the original infectious focus. Such may have taken place in Case 1, described in this paper. It is evident from the history

that in 1906 he suffered from a very severe infection, the nature of which is not evident from the patient's description nor from the post-mortem examination. The appearance of the symptoms in the joints and bones which were observed by the patient two years subsequently makes it seem probable that these were induced by this acute illness. The earlier disease, however, entirely disappeared, leaving no traces of its nature, while the osteo-arthropathy irregularly but gradually advanced. The malignant disease of the left lung found at necropsy may have existed longer than would be indicated by the history, but repeated roentgenograms failed to demonstrate any abnormal process in the lungs until 1913, while the patient observed the first signs of the osteo-arthropathy in 1908.

We are justified, I believe, in taking the grounds that the six cases just cited suggest the possibility only of a primary form of osteo-arthropathy. If such a type does exist, it is indeed strange that among the large number of cases in the literature none is to be found which is indisputably primary. On the other hand, as Brooks states, one is struck with the constancy of evidence that hypertrophic osteo-arthropathy is the result of some primary disease.

The considerable number of post-mortem examinations on cases of this disease together with Roentgen-ray studies during recent years leaves no question as to the essential features of its pathology. So far as the skeleton itself is concerned, the changes consist primarily in a slowly progressive, ossifying periostitis beginning usually in the distal ends of the diaphyses of the bones of the forearm and lower legs, later involving also the other bones of the limbs and even in some cases nearly all the remaining bones of the skeleton. Later in the course of the disease and coincident with the periosteal proliferation, there is also a rarefying osteitis of the shafts with fatty changes in the marrow. Various authors of recent years seem to be in agreement as to the exact nature of the histological changes taking place, and these need not be discussed here. A study, however, of a series of cases over a long period of years by means of frequent Roentgen-ray examination has afforded the author an opportunity for close observation as to the extent of the affection of the bone in advanced stages of the disease and the changes which take place at various periods.

In the first place, it does not appear to be generally recognized that the changes in the skeleton in a well developed case of secondary hypertrophic osteo-arthropathy are seldom confined to the bones of the forearms, hands, lower legs and feet as so often described. In Case 1, for example, the alterations were almost general. In fact, it may be stated that a Roentgen-ray examination in these cases always reveals skeletal changes of greater extent and of a more marked type than is at first evident.

In his original paper, Bamberger<sup>13</sup> says that in the long existing cases the periostitis ossificans leads to thickening and condensation of the cortex and that here we have a later stage of the process which is seldom seen because in most instances the primary disease has led to death earlier. This transformation has been observed several times in the cases described above. While at first the new subperiosteal bone is sharply differentiated from the old shaft, at a later period, that is, usually after a lapse of two or three years, the two become more or less fused and in most places are indistinguishable. Judging from our own observations only, this transformation appears to occur in those cases which remain more or less stationary as well as in those which have a chronic progressive course. Accompanying this fusion just mentioned in the late stages of the disease, the entire structure of the bones, especially those most involved, becomes entirely altered. In the most extreme cases there remains scarcely any of the appearances of the original bone. Instead the osseous tissue appears very thin and of a coarse, irregular structure, in general very closely resembling the appearances seen in typical cases of osteitis deformans. I have never seen, however, any curving of the bone or deformity, except in outline, as is so characteristic in this latter disease. As a late manifestation, I have once or twice seen evidences in individual bone of a characteristic atrophy, although as a rule the process is primarily one of hypertrophy. These changes just described are admirably shown in Figures 5, 6, 7 and 8.

The statement made by most authors that the changes in the bones are confined essentially to the diaphysis is wide of the truth. While the process does probably invariably begin in the diaphysis as shown in Figure 10, yet all well-established cases show a very marked new formation of bone in the epiphyseal portion. It is usually much less regular than the sheath about the diaphysis and apparently much less rich in lime salt, appearing as a mossy, faint deposit in the roentgenogram, which most commonly stops abruptly at the line of the joint surface. This is well indicated in Figures 5, 6 and 8. These latter changes closely resemble, or are even identical with, the appearances seen in cases of acromegaly.

The Roentgen-ray examinations of the first four cases indicate very clearly that the process in the bones follows a course parallel to the slowly progressive clinical course. That the almost extraordinary diminution in the size of the affected parts which has so often been observed during the periods of remission, is due primarily to changes in the soft tissues rather than the bones, cannot be doubted, but in three of my cases (Cases 2, 3 and 4) there has been observed after varying periods an unmistakable retrogression in the bony growth which has led to a slight diminution in the size of the bones themselves.



There is an almost complete unanimity of opinion among authors on this subject, that the clubbing of the fingers and toes in cases of secondary hypertrophic osteo-arthritis is due entirely to changes in the soft parts. I have found but three writers who record changes found in these bones by the Roentgen ray. Gouldsbrough<sup>74</sup> states that in his cases there was definite proliferation in the distal phalanges. Tcleky<sup>155</sup> says that increase in the size of these bones is rarely seen, and reports one case in which the Roentgen ray showed a slight deformity of two only. In a single case, Kruger<sup>65</sup> demonstrated mossy deposits in the diaphysis of the end phalanges. In my cases more or less marked changes were found in all five. In two they were slight, but in the remaining three very noteworthy (Figure 9). The changes noted in these five cases consisted essentially in a proliferation of the distal half of the last phalanges, usually giving the "burr form," but occasionally with immense burr-like processes as seen in Figure 9.

Considerable controversy has centered about the question of the pathological processes accompanying the constant and usually striking objective signs in the joints adjacent to the affected bones. Many of the older writers have claimed that the changes were entirely confined to the periarticular tissues, the interarticular cartilage always remaining intact and unchanged. The more recent writers are largely in accord in their description of the pathology of the joints, and nearly all admit that besides the thickening of the periarticular tissues and the presence of effusion, there are, at least in the most developed cases, changes in the cartilage as well. It is commonly more or less eroded and in rare instances has entirely disappeared. Reynaud and Audibert,<sup>153</sup> and Ball and Alamartine<sup>11</sup> describe true osteophytes as occasionally occurring and even a considerable degree of ankylosis as a result. All of these lesions have been present in my cases, and, clinically, the severe symptoms and disability have been due largely to the conditions in the joints. In Case 1, for example, for a long time at the beginning the symptoms were entirely confined to the joints, and throughout the course of the disease the symptoms were referred very largely to these parts.

Several authors have in individual cases described a marked irregularity in the course of the disease which my observations on four of the above cases followed for a considerable time seem to show to be characteristic. It is a common observation that cases of simple clubbing occurring secondary to such diseases as empyema, quickly return to normal size and appearance after the evacuation of the pus. Only a few cases of hypertrophic osteo-arthritis, however, are on record in which similar changes have taken place, and only a few of these were observed by the Roentgen rays with reference to the possible

participation of the bones in this retrograde process. Thompson<sup>191</sup> lays particular emphasis on the fact that clubbing may entirely disappear with improvement in the primary disease, but states that there is no evidence that absorption of the newly-formed bone ever occurs. In Gillett's<sup>71</sup> case considerable improvement in the fingers and toes followed almost immediately the drainage of the empyema, but the condition in the bones was not studied by means of the Roentgen rays. Thorburn<sup>193</sup> likewise in one case of phthisis with cavity, after drainage, and a second of empyema, after operation, speaks of retrogression in the clubbing of the fingers. Godlee's<sup>73</sup> case of bronchiectasis and empyema developed clubbing after four months, which disappeared ten weeks after the cessation of expectoration. Schittenhelm<sup>162</sup> studied his case by means of skiagrams and found that the diminution in the swelling was confined entirely to the soft parts, the affected bones remaining unchanged. Alexander<sup>3</sup> notes an improvement following the improvement in the primary bronchiectasis. At the time the case was published the lung condition was practically normal and the joint symptoms and swelling had entirely disappeared. The bones did not seem enlarged and skiagrams showed that the new bone had become more dense and so closely fused with the old shaft that the line of division was only to be made out in places. These changes in the bones are evident in Plates III and IV of his article. The author speaks of this as a unique case. Relief of symptoms in the joints and the pain in Botez's<sup>24</sup> case of bronchiectasis and gangrene of the lungs followed the treatment of the lung condition. Likewise in Barot and Pichard's<sup>15</sup> case, the improvement in the pneumonia following treatment resulted in an improvement in the general condition and especially the joint symptoms.

In Case 5 of my series, no opportunity was offered to study the course of the disease as the patient was under observation only a few days; but in the other four which were studied for a period of years there was a very extraordinary variation in their course. In Cases 2, 3 and 4 the alternating periods of exacerbation and retrogression constantly followed an increase or diminution in the activity of the primary disease. The course in Case 1 is most interesting. Exactly the same variations were noted throughout the period of nearly six years while under observation, although no primary disease was ever found. At times the symptoms in the joints were very acute and accompanied by enormous swelling and stiffness, with evident increase in the degree of clubbing of the fingers and toes. Following these periods there were intervals of weeks or months when the symptoms of pain almost entirely disappeared and the swelling and clubbing diminished materially. The bones were studied at frequent intervals

during the entire period of observation by means of the Roentgen rays and never gave any evidence whatsoever of any retrogression in the bony changes, though for considerable periods coincident with the remissions in the clinical course, the process appeared to be at a standstill. As stated in the history of the case, the explanation of this is probably found in the fact that the disease ran a chronic and irregularly progressive course. As in Alexander's<sup>3</sup> case, the new bone in many cases became closely fused with the old, but never less in thickness. The course of the process in Case 2 is especially noteworthy. On March 24, 1913, the patient was readmitted to the hospital apparently in a dying condition. There was a generalized tuberculosis involving both lungs, with signs of a large cavity on the left and a very abundant putrid expectoration. There was also cardiac decompensation and a tuberculous enteritis. Signs of the osteo-arthritis were very striking and much more marked than previously. After a year's residence in the hospital, the patient showed the extraordinary improvement in general condition which sometimes occurs in advanced pulmonary tuberculosis. The enteritis had entirely disappeared, the heart had become perfectly compensated, and the condition in the lung essentially quiescent. The sputum, likewise, had practically entirely disappeared. All the symptoms and signs in the arms and legs showed a corresponding and surprising improvement. There was still slight enlargement of the lower forearms and lower legs, with slight swelling of the wrists, ankles and knees and a moderate clubbing in the fingers and toes. The changes previously noted in the bones of the hand and especially in the terminal phalanges had literally almost disappeared. The layer of periosteal new bone in the forearms and legs was much thinner, more dense and, except in a very few places, formed a part of the original shaft. In this case, then, there was an unmistakable process of resorption. Exactly the same type of retrogression in the newly formed osseous tissue was observed in Case 3. Case 4 has been under observation for eleven years. During the first year of this period the patient was operated on for the empyema, which promptly healed and he has had no return of symptoms. For the past nine or ten years the bronchiectasis has been quiescent and the patient at work constantly, seemingly in good general health. The condition of osteo-arthritis has apparently remained absolutely unchanged. There are no symptoms in the joints or long bones. During the first few years there was unmistakable evidence in the roentgenograms of a process of retrogression in the bone, but during recent years they have remained unchanged.

From these observations it seems fair to conclude that there is in hypertrophic osteo-arthritis a characteristic irregular clinical course

with exacerbations and remissions following increased activity or improvement in the primary disease. These fluctuations in local signs are largely due to changes in the soft parts, although it is probable that in many instances a similar variation, but of less marked degree, takes place in the osseous tissue as well. It is possible that in some of the early cases perhaps of the acute type, the bones, if not too much affected, may, with the cure of the primary disease, return to their normal size. It is probable, as Lemerrier<sup>103</sup> suggests, that when the osteo-arthritis has passed the first stage, the retrogression is never complete. There can be little doubt that in a large number of cases, following the cure of the antecedent disease, the osteo-arthritis becomes in a strict sense quiescent. Case 1 of my series suggests that rarely the disease, once well established, may continue progressive quite independently of the original disease focus.

The rôle played by pulmonary tuberculosis as a cause of hypertrophic osteo-arthritis has been frequently discussed and several authors have commented on the relative infrequency with which osteo-arthritis occurs in association with this disease. Alexander<sup>3</sup> collected seventy-seven typical cases of hypertrophic osteo-arthritis from the literature and among them found fifteen of pulmonary tuberculosis, or 19 per cent. Janeway<sup>88</sup> collected ninety-three typical cases, sixteen associated with pulmonary tuberculosis, or 17 per cent. Wynn<sup>218</sup> found one hundred cases with eighteen, or 18 per cent. of tuberculosis of the lungs. The literature to date contains 139 cases which, with the five here recorded, make a total of 144, of which thirty followed pulmonary tuberculosis, or 20 per cent. Three of the five patients here reported were suffering from this disease. These more recent figures distinctly emphasize the importance of pulmonary tuberculosis in the etiology of osteo-arthritis. The explanation of the fact that pulmonary tuberculosis, which is such a common disease of the lung, in comparison with bronchiectasis, which is more frequently the cause of osteo-arthritis, is perhaps found, as Thompson suggests, in the fact that in pulmonary tuberculosis there is usually but a slight degree of toxemia, and the fact that the secretions from the lungs are easily raised and therefore not so effective as in the case of bronchiectasis as foci of infection. Figures from Groups B, C and D reported in this paper still further emphasize the importance of pulmonary tuberculosis as the etiological factor in the disease under discussion. In all, among the thirty-nine miscellaneous cases studied, nineteen were pulmonary tuberculosis, and of these six showed changes in the long bones typical of osteo-arthritis, or 50 per cent. of Group C which showed the lesions of osteo-arthritis. If simple clubbing of the fingers is to be considered as merely an early stage of

osteo-arthropathy, as I believe can be shown from a study of these groups, then tuberculosis of the lungs will take first place in the list of diseases inducing these bone and joint changes.

THE RELATIONSHIP OF SIMPLE CLUBBING TO SECONDARY HYPERTROPHIC  
OSTEO-ARTHROPATHY

Although much has been written concerning the possible relationship of these two conditions, writers on the subject are far from an agreement, and it must still be regarded as an open question. The confusion in the literature is evident from the fact that although most authors restrict the term secondary hypertrophic osteo-arthropathy to those cases showing alterations in the long bones as well as clubbing of the fingers, a considerable number of cases of simple clubbing of the fingers have been reported as examples of this disease. By far the majority of authors consider these two conditions at least closely related if not identical. Bamburger<sup>13</sup> published three cases in which there were no changes except the hippocratic fingers, but which at post mortem examination were found to have periostitis of the long bones, and concludes from his observations that the clubbing in the distal phalanges is simply the first stage of osteo-arthropathy and that both conditions are co-effects of the primary disease. Marie<sup>113</sup> believes that the hippocratic fingers seen with various lung diseases are not essentially different from those observed with osteo-arthropathy. Lefebvre<sup>99</sup> argues that both are phenomena of the same order. Thompson<sup>102</sup> maintains that a common cause exists for both and that the drumstick fingers are simply the initial stage of osteo-arthropathy. Landis<sup>95</sup> argues that since both are associated with the same primary conditions, that osteo-arthropathy is always accompanied by clubbing of the fingers and toes, and that some cases of simple clubbing have shown changes in the long bones, this should be regarded as an incipient or arrested stage. Wynn,<sup>218</sup> in the conclusion of a long discussion, says "One is forced, I think, to the conclusion that simple, ordinary clubbing is but the early stage of the condition which in later stages is termed osteo-arthropathy. It is produced by a lesser action of the same causes, which are probably toxic." Janeway<sup>88</sup> is of the opinion that they are different stages of the same process. Lemerrier<sup>103</sup> regards club fingers as an abated form of osteo-arthropathy or the latter in process of evolution. Essentially the same view of the close relationship between these two conditions is held by various other authors including Rauzier,<sup>146</sup> Walters,<sup>210</sup> Géraud,<sup>65</sup> Reynaud and Audibert,<sup>153</sup> Möbius,<sup>124</sup> Vedel,<sup>203</sup> Villard,<sup>206</sup> Comby,<sup>30</sup> Teleky<sup>185</sup> and others. Rendu and Bouloche,<sup>131</sup> on the other hand, are emphatic that hypertrophic osteo-arthropathy should not be confounded with digital deformities

occurring with other diseases, especially those producing cyanosis. Genova<sup>64</sup> contends that an essential difference exists between the two. Labrit<sup>97</sup> believes them to be independent conditions. Bécclère<sup>17</sup> and Dennig<sup>15</sup> found no osseous lesions in their cases of hippocratic fingers and therefore maintain that this condition is distinct from hypertrophic osteo-arthritis. Bezancón and Jong<sup>20</sup> made an exhaustive study of the subject and differentiate the two conditions as follows: First, in hippocratic fingers the process is always limited to the end phalanges, irrespective of the length of the causal diseases, while in osteo-arthritis there are always multiple deformities of the bones and joints; second, pain and functional immobility, which are always present in the latter condition, are never seen in the former; third, pathological changes in simple clubbing consist entirely in hypertrophy of the soft parts, while in osteo-arthritis lesions are osseous, articular and periosteal; fourth, no case of osteo-arthritis is recorded which began as simple clubbing. They conclude that the two conditions have no relation to each other.

In an effort to settle this question, I have, during the past few years, studied a miscellaneous group of thirty-nine cases of simple clubbed fingers occurring with a considerable variety of diseases. A summary of these cases together with the results of Roentgen-ray examination and grouped according to the osseous lesions found, are given below.

*Group B.—Twenty-Two Cases of Simple Clubbing with Changes Confined to Soft Parts\**

CASE 6.—F. A., male aged 20, Boston Consumptives' Hospital, March 26, 1914.

Chronic pulmonary tuberculosis, Stage III, with large cavity in left upper lobe. Symptoms marked, with dyspnea and cyanosis.

Marked clubbing in fingers and toes.

CASE 7.—H. B., boy, aged 18. Patient under observation for the past ten years. Chronic abscess of left lower lobe, with typical signs, but very few constitutional symptoms. Patient in good general condition, at regular occupation and no symptoms except slight cough with occasional raising of moderate amount of rather foul sputum.

Fingers and toes moderately clubbed.

CASE 8.—B. C., man, aged 39, Boston Consumptives' Hospital, Oct. 31, 1909.

Empyema with operation ten years ago; sinus still discharging. Old Pott's disease. Chronic pulmonary tuberculosis, Stage III. Patient, although not confined to bed, is very weak and emaciated. There is moderate dyspnea with exertion, but no cyanosis. Never noted any changes in the ends of the fingers, but for past two years has had nearly constant dull pains in the lower legs and the bones have been sensitive.

\* Systematic Roentgen-ray examination in each case failed to show any abnormalities in the distal phalanges, long bones or joints.



The ends of the toes and fingers are all strikingly clubbed, but without marked cyanosis or injection of the nail bed. The forearms appear normal but the lower legs are possibly a little enlarged, although the bones feel normal.

CASE 9.—W. C., woman of 50, Long Island Hospital, seen March 16, 1910.

The patient in last stages of pulmonary tuberculosis and confined to bed. Extensive process in lungs, with cavity formation.

Only slight clubbing of fingers and toes.

CASE 10.—A. D., a bartender aged 41, seen at the Boston City Hospital August 5, 1910.

Chronic alcoholism; cirrhosis of the liver with ascites; chronic pulmonary tuberculosis, Stage III. The patient is emaciated and very weak; considerable dyspnea.

All the fingers show moderate clubbing, which is most marked in the thumb and the next two fingers. Feet are similarly affected.

CASE 11.—J. E., man aged 32, seen at Long Island Hospital March 21, 1910.

Chronic pulmonary tuberculosis without cavity formation. Slight clubbing of fingers and toes.

CASE 12.—G. G., man aged 50, seen at Boston Consumptives' Hospital March 1, 1914.

Chronic pulmonary tuberculosis, Stage III, with cavity formation; marked toxemia. Considerable dyspnea and cyanosis. Recent severe hemorrhage.

Moderate clubbing of fingers and toes.

CASE 13.—E. K., man aged 40, seen at the Long Island Hospital March 19, 1910.

Pulmonary tuberculosis, Stage III; mitral stenosis and regurgitation; chronic alcoholism.

The fingers and toes show only a slight degree of clubbing.

CASE 14.—T. F. K., man of 30, entered the Boston City Hospital December 15, 1913.

Malignant endocarditis, with positive blood cultures on April 24, 1914. Death a few days later. No necropsy.

Clubbing of fingers and toes developed while under observation in the hospital and became fairly well marked.

CASE 15.—A. L., man aged 32, seen at the Long Island Hospital April 16, 1914.

Typical case of advanced pulmonary tuberculosis with extensive cavity formation; ambulatory, but in an extremely weak condition, with considerable dyspnea and some cyanosis.

All the fingers and toes are strikingly clubbed and the hands and feet appear clumsy and thickened.

CASE 16.—J. J. M., man aged 42, admitted to the Boston City Hospital April 19, 1910.

Pulmonary tuberculosis, stage III, with severe symptoms; chronic alcoholism.

Clubbing of the fingers and toes of moderate degree.

CASE 17.—T. P. M., man aged 33, seen at Boston Consumptives' Hospital April 24, 1914.

Pulmonary tuberculosis, stage III, without signs of cavity formation. Considerable cyanosis and dyspnea.

Moderate clubbing of fingers and toes.

CASE 18.—A. R., male aged 70, seen at Long Island Hospital March 21, 1910. Arteriosclerosis; apoplexy; senile dementia; emphysema with marked dyspnea and cyanosis; no temperature. Patient died May 1, 1910.

Very moderate clubbing in fingers and toes.

CASE 19.—J. S., man aged 44, seen at the Long Island Hospital March 21, 1910.

Chronic alcoholism; chronic pulmonary tuberculosis with cavity formation; chronic interstitial nephritis; probable old syphilis. Patient died Oct. 21, 1910. No necropsy.

Moderate clubbing of fingers and toes.

CASE 20.—J. S., a woman aged 31, entered the Boston City Hospital April 13, 1913.

Chronic jaundice due to probable malignant disease of the liver; extreme emaciation with marked dyspnea. Lungs and heart normal. Patient died May 6, 1913. No necropsy.

Moderate clubbing of fingers and toes.

CASE 21.—P. S., man aged 21, seen at the Boston City Hospital May 6, 1913.

Aortic regurgitation and stenosis; chronic nephritis. Severe hemorrhage from gums and mucous membrane, with resulting extreme anemia. Unusually severe dyspnea with the slightest exertion.

Moderate clubbing of all the fingers and toes.

CASE 22.—A. S., male aged 59, seen at Boston Consumptives' Hospital March 5, 1914.

Chronic pulmonary tuberculosis, stage III, with extensive but inactive process. Occasionally some cyanosis of fingers.

Moderate clubbing of fingers and toes.

CASE 23.—J. C. S., male of 68, seen at Long Island Hospital March 20, 1910. Asthma since 12; mitral regurgitation with hypertrophy and dilatation of the heart; eczema; chronic interstitial nephritis; arteriosclerosis.

Moderate clubbing of fingers and toes.

CASE 24.—C. T., woman aged 22, entered Boston City Hospital April 1, 1910. Infection with colon bacillus; septicopyemia and pyonephrosis.

Slight clubbing of fingers and toes developed while patient was under observation in the hospital. Nails deeply cyanosed.

CASE 25.—A. N. V., a boy aged 16, entered Boston City Hospital Dec. 23, 1913.

Pneumonia with complicating endocarditis and pericarditis. High, irregular temperature with marked dyspnea and anemia. Some cyanosis of the extremities.

Moderate clubbing of the fingers and toes, where the changes seem to be largely in the soft parts.

CASE 26.—T. W., a boy aged 4, entered the Boston City Hospital May 9, 1914, service of Dr. Lothrop.

Abscess of left lung since one year old, with very severe, persistent, spasmodic cough accompanied by a large amount of mucopurulent, occasionally bloody and moderately foul sputum. Fever and night sweats. Extensive and marked signs of cavity in the left chest.

The fingers and toes show a striking and typical condition of clubbing.

CASE 27.—R. W., a boy aged 11, entered Boston City Hospital Nov. 16, 1906.

Bronchiectasis with typical cough and sputum following pneumonia four years previously.

Jan. 26, 1910. The fingers and toes show a moderate degree of clubbing, although considerably less than formerly.

#### *Group C.—Five Cases of Simple Clubbing with Changes in the Distal Phalanges*

CASE 28.—M. B., woman aged 40, Long Island Hospital, Feb. 13, 1909.

Chronic pulmonary tuberculosis, stage III, without signs of cavity. Patient died Jan. 23, 1912. No necropsy.

No alterations in the limbs except a slight degree of clubbing in the fingers and toes.

Roentgen-ray examination March 16, 1910. The distal phalanges of the hands show a slight proliferation in their outer half. The remaining bones of the skeleton and the joints were not examined.

CASE 29.—A. K., woman aged 61, seen at the Long Island Hospital March 16, 1910.

Chronic pulmonary tuberculosis without signs of cavity.

Characteristic clubbing of the fingers and toes of moderate degree.

Roentgen-ray examination March 16, 1910. Hands and forearms only. Considerable proliferation of the distal phalanges. Otherwise the bones and joints are normal.

CASE 30.—B. K., female aged 65, entered Long Island Hospital July 28, 1910.

Chronic bronchitis; chronic nephritis; arteriosclerosis with aortic roughening and mitral insufficiency. In August, 1910, an attack of pneumonia with delayed resolution. Died April 27, 1911. No necropsy.

Moderate clubbing of the fingers and toes.

Roentgen-ray examination Oct. 10, 1910, of hands and forearms only. The only abnormality made out is a moderate proliferation in the distal half of the last row of phalanges of the hands.

CASE 31.—N. McG., man aged 54, seen at Long Island Hospital March 19, 1910.

Pulmonary tuberculosis, stage III; arteriosclerosis with mitral insufficiency.

Moderate clubbing of the fingers and toes.

Roentgen-ray examination March 19, 1910, of hands and forearms only. The outer end of the distal phalanges are moderately ragged and show a marked proliferation. Arteries in the forearm show high degree of calcification. Joints normal.

CASE 32.—H. N., man aged 29, entered the Massachusetts General Hospital, service of Dr. R. C. Cabot, May 7, 1914.

Acute symptoms of nephritis with signs of old mitral stenosis and regurgitation, with decompensation and purpura. Marked edema of legs. No cyanosis.

The fingers and toes show a condition of marked clubbing, the type in the former being quite unique. The enlargement involves the entire last phalanx of the fingers, the swelling extending well down over the distal joint. In contrast to the usual rounded ends of the fingers they are almost square as though chopped off. The nails are unusually broad, a little thickened, and ribbed longitudinally, but are exceedingly short, in some instances being less than one-half inch. They do not present the usual parrot-beaked type.

Roentgen-ray examination May 12, 1914. The outer half of all the distal phalanges of the hand show a slight but definite proliferation of bone, the fan-shaped ends appearing more ragged and expanded than normal. On several of these phalanges of each hand at the joint end are small osteophytes resembling those seen in early osteo-arthritis. The joints, however, show no abnormal appearances. The bones of the forearms are likewise normal.

#### *Group D.—Twelve Cases of Simple Clubbing with Changes in the Long Bones*

CASE 33.—R. B., male aged 38, Boston Consumptives' Hospital, March 27, 1914.

Advanced pulmonary tuberculosis; fibrosis without cavities. Very weak and emaciated; marked dyspnea and considerable cyanosis.

All the fingers and toes show moderate clubbing.

Roentgen-ray examination March 27, 1914. There are no clearly marked changes in the distal phalanges of the hand, but the other two rows are slightly thickened to a varying degree and in places show small but definite osteophytes. The right radius and ulna show a thin, subperiosteal deposit along the inner side of each for approximately the lower third. Similar changes are seen in the ulna and radius of the left forearm, but of lesser degree.

CASE 34.—A. E., a 32-year-old man, seen at the Boston Consumptives' Hospital, April 16, 1914.

Very advanced pulmonary tuberculosis without signs of cavity formation; febrile.

Very moderate clubbing of fingers and toes.

Roentgen-ray examination April 16, 1914. Bones of the arms and hands normal. The end phalanges of both feet are very irregular and show osteophytic outgrowths which are distinctly more than normal. In both feet the second, third and fourth of the first row of phalangeal bones show slight, somewhat irregular cortical deposits along the shaft. On the right similar changes are shown on the outer side of the first. The bones of the lower legs are normal.

CASE 35.—M. G., male aged 45, seen at the Boston Consumptives' Hospital April 14, 1914.

Very advanced pulmonary tuberculosis with extensive cavity formation; dyspnea and cyanosis striking.

Moderate clubbing of fingers and toes.

Roentgen-ray examination April 24, 1914. Beyond a very slight roughening in a few places along the first row of phalanges, nothing abnormal is noted in the bones of the hands. Feet normal except for marked enlargement and irregularity in the distal half of the last phalanx of one great toe. Along the outer side of the left tibia in its lower half there is a thin layer of cortical new bone and a similar layer along the inner side of the fibula for an extent of about 2 inches below the head. This latter deposit is ragged in outline and evidently contains almost no lime salts. The other bones of the limbs are not abnormal. Joints normal.

CASE 36.—G. C. P., a man aged 32, seen at Boston Consumptives' Hospital April 16, 1914.

Advanced pulmonary tuberculosis with cavity formation; extreme dyspnea with considerable cyanosis.

Marked clubbing of fingers and toes.

Roentgen-ray examination April 16, 1914. The distal phalanges are all strikingly changed, the normal fan shape being greatly exaggerated, the outlines extremely irregular. No other bones of the hands are altered. The distal phalanges of the feet seem a little more broad and irregular than normal. Both tibiae show a thin, irregular deposit of new bone varying from one-sixteenth to one-eighth of an inch in thickness along the inner side of nearly the entire upper half. The bones of the forearms show no abnormalities. Joints likewise normal.

CASE 37.—S. S., man aged 36, seen at Boston Consumptives' Hospital April 7, 1914.

Last stages of pulmonary tuberculosis with extensive cavity formation.

Marked clubbing in fingers and toes.

Roentgen-ray examination April 24, 1914. Bones of the hands and feet and forearms are normal. The right tibia along its outer surface from the epiphyseal line above nearly throughout half its extent shows a new layer of bone beneath the periosteum which in its thickest portion is about one-eighth of an inch. The left tibia shows a similar condition, but less well marked, for about one-third of its length only. The left tibia also in one place for a distance of about one inch shows a thin, irregular new layer. Fibulae normal.

CASE 38.—T. B. G., man aged 33, seen at the Boston City Hospital Dec. 27, 1910.

Severe bronchial asthma since ten; chronic bronchitis; chronic alcoholism; myocarditis. Considerable cyanosis of the extremities and marked edema of the lower legs.

A slight degree of clubbing in fingers and toes.

Roentgen-ray examination March 21, 1911. All of the end phalanges of the feet show a very unusual broadening out and are irregular in outline; the end

phalanges of the fingers somewhat less changed. Nearly all of the first row of phalanges of the hands show an irregular thin deposit of bone just beneath the periosteum. The long bones of the forearms and lower legs are negative. Joints normal.

CASE 39.—J. P. J., man of 28, seen at the Boston Consumptives' Hospital April 24, 1914.

Typical history of bronchiectasis since the age of 10, with signs of large cavity in the right lung; several attacks of pneumonia since, the last two years ago. Pulmonary tuberculosis which has apparently developed in the past few years. Lost left leg when 8 years old.

Never any symptoms in legs or arms or in joints until the past few months, when he has had slight swelling of the ankles, knees and wrists, with moderate dull pain and slight sensitiveness to pressure in these regions, especially over the bones.

Very striking clubbing of all the fingers and toes. The ankles, knees and wrists are slightly swollen, but no definite enlargement made out in lower legs and forearms.

Roentgen-ray examination April 24, 1914. Terminal phalanges of the hand very ragged, with definite proliferation of bone. Second row of phalanges in the fourth and fifth show very slight subperiosteal deposit of bone, more marked on the outer side. The first row shows slight but evident changes of this nature throughout, most marked on outer side. All the metacarpal bones show still more marked changes of this type, most evident in the thumbs. The ulnae and radii show definite characteristic deposits of bone beneath the periosteum, in one place on the right ulna approximately a quarter of an inch in thickness, the changes being mainly confined to the distal half, although in the right ulna throughout. In the lower portion of the diaphyses of the humeri a thin new layer easily made out. The carpals normal and no changes found in the joints of the arms and wrists.

The terminal phalanges of right foot not well shown, except the great toe, in which there is marked proliferation of bone. Second row of phalanges are normal, except for the great toe, which shows a thin layer throughout the shaft. Only the fourth and fifth of the first row show characteristic changes. Tarsus normal. The right tibia seems considerably enlarged, appearing massive throughout, but in many places no distinction is evident between the old cortex and the new layer of bone. Externally, however, the new shaft of bone can be easily traced through the two-thirds of the diaphysis from proximal end down: at about the middle of the tibia the new layer is a quarter of an inch in thickness. Down over the internal condyle there is a considerable formation of irregular new bone. At the head of the tibia there is considerable proliferation of bone of the same type from the epiphysis to the joint surface. Right fibula externally has a marked deposit of bone almost throughout its entire length, showing best in the middle third, where there is an irregular deposit varying from one-sixteenth to one-eighth inch in thickness. The ankle and knee joints present no abnormalities.

CASE 40.—J. B., man aged 41, Boston City Hospital, May 20, 1910. Aortic and mitral disease with decompensation, anasarca; moderate cyanosis of the extremities; extreme dyspnea.

Since January, 1910, both knees and ankles have been considerably swollen and moderately painful, but without redness or tenderness. Patient died June 7, 1910. No necropsy.

The fingers and toes show marked clubbing.

Roentgen-ray examination May 2, 1910. The phalanges show no definite changes, but in all the metacarpal bones of the hand there is a thin subperiosteal layer of new bone. The ulna and radius of both forearms show the characteristic cortical new bone as a thin, somewhat irregular layer in the dis-



tal portion of the diaphyses. None of the bones of the feet is abnormal except that the fifth metatarsal in each shows a thin cortical layer throughout the entire shaft. The fourth metatarsal likewise shows a thin layer on its outer side. Approximately the lower third of the tibiae and fibulae show alterations like those described in the ulnae and radii. No changes in the joints are to be made out.

CASE 41.—J. L., man of 52, entered Boston City Hospital Jan. 14, 1910.

Chronic alcoholic; gonorrhea and chancroids many times but no history of lues; aortic regurgitation. Patient died Jan. 12, 1911, of cerebral hemorrhage.

All the fingers are markedly clubbed, especially on the right hand, and the feet show moderate changes of this nature.

Roentgen-ray examination Jan. 13, 1910. The end phalanges of the feet seem slightly more fan-shaped and ragged than normal, but the changes are not definite. Along the inner side of the left ulna in its upper third there is a definite thin, even layer of new cortical bone. Similar changes, but of much more marked degree, are seen in the right ulna and extending from the upper end to the junction of the middle and lower third. On its outer side and near the lower end there are a few thin, irregular deposits. Otherwise the bones of the skeleton are normal and the joints show no changes.

CASE 42.—J. M., bartender aged 41, Boston City Hospital, April 21, 1914.

Chronic alcoholism; cirrhosis of the liver; extreme dyspnea and ascites with considerable edema of the lower legs. No cyanosis, although nails are deeply injected.

Moderate clubbing of fingers and toes, most marked in thumbs and great toes.

Roentgen-ray examination April 21, 1914. Hands, feet, forearms and joints show no changes. Right fibula in upper portion both along inner and outer surface for a distance of 2 or 3 inches shows an irregular thin deposit, stopping sharply at the epiphysis. Similar changes are found in the left fibula. The outer border of the tibiae in several places is distinctly roughened, but no new layer of bone can be made out.

CASE 43.—H. C. S., woman aged 35, seen at the Massachusetts General Hospital, March 15, 1914, service of Dr. C. L. Scudder.

Paroxysmal cough for one year with large amount of greenish-brown, at times very foul, sputum. It is sometimes brought up in large amounts with change of position. Dyspnea with exertion.

Operation March 27, 1914; a large amount of foul pus evacuated from the left pleural cavity.

The fingers show a rather marked condition of clubbing; the toes also, but somewhat less.

Roentgen-ray examination March 16, 1914. Feet and legs not examined. Along the outer side of the metacarpal bone of the right thumb there is a definite thin subperiosteal layer of new bone. Similar changes in the lower left radius and ulna.

CASE 44.—J. E. T., an electrician aged 50, seen at the Massachusetts General Hospital April 15, 1914, service of Dr. C. L. Scudder.

Chronic tuberculosis of shoulder joint with pulmonary tuberculosis of twenty years' standing. Process evidently of fibroid type. No fever, cyanosis or dyspnea.

The fingers and toes show a moderate condition of clubbing.

Roentgen-ray examination April 17, 1914. The bones of the hands are normal except for a slight proliferation in many of the distal phalanges. The cortex of the tibia in several places is definitely thickened and slightly irregular in outline, but the line of separation between the old cortex and the new subperiosteal bone is not always to be made out. The bones of the forearm and the joints are normal. Roentgenograms of the feet not made.



The clubbing in the fingers and toes is said to be much less marked than in previous years. If this observation be correct, it is undoubtedly explained by the fact that the process in the lung is apparently quiescent, and that some time ago the infectious focus in the shoulder was obliterated through a section of the upper end of the humerus.

A summary of the results in these groups is given in Table 2.

TABLE 2.—RESULTS OF ROENTGEN-RAY EXAMINATION IN THIRTY-NINE CASES OF SIMPLE CLUBBING OF FINGERS AND TOES

Disease	Bones Normal	Changes in Distal Phalanges Only	Changes in Long Bones	Totals
Pulmonary tuberculosis...	10	3	6	19
Bronchiectasis .....	3	..	2	5
Bronchial asthma, bronchitis .....	..	..	1	1
Bronchial asthma, mitral disease .....	1	..	..	1
Emphysema .....	1	..	..	1
Chronic bronchitis, mitral disease .....	..	..	..	1
Cardiac disease .....	2	1	2	5
Cardiac disease, pulmonary tuberculosis .....	1	1	..	1
Cirrhosis liver .....	..	..	1	1
Cirrhosis liver, pulmonary tuberculosis .....	1	..	..	1
Chronic jaundice (malignant disease liver ?)....	1	..	..	1
Septicemia .....	2	..	..	2
	22	5	12	39

An examination of Table 2 shows that twenty-two of the total thirty-nine cases, or 56.4 per cent., showed no changes in the distal phalanges or long bones, while five, or 12.8 per cent., showed alterations of varying degree in the ungual phalanges, and twelve, or 30.8 per cent., had periosteal proliferation in the long bones. Of this last group, six only showed ungual proliferation. A careful examination of these individual cases affords no explanation for these results; neither does the study of the primary condition yield anything significant. Furthermore, the degree of clubbing does not seem to correspond, except in a very general way, to the radiographic findings. The cases of Group D do on the whole present a more marked degree of clubbing than the other two. Bamberger,<sup>13</sup> Landis,<sup>98</sup> Reynaud and Audibert<sup>153</sup> and Teleky<sup>185</sup> mention cases showing proliferation in the end phalanges, but the changes in clubbed fingers are usually described as being confined entirely to the soft parts. The fact that eleven of

the above series of thirty-nine cases, or 28 per cent., have changes in these bones, would seem to prove definitely that the osseous tissue does participate in the changes to a far greater degree than is ordinarily supposed. The type of alteration is a definite and constant one, being usually confined to the distal half of the phalanx and consisting in an irregular hypertrophy of the bone, which in the most marked cases has a burr-like appearance, or, as one author has described, "a picture not unlike that of an electro magnet which has been dipped in fine iron filings." These appearances, both in type and distribution, seem to me exactly similar to those which have been observed in the end phalanges of the five cases of true hypertrophic osteo-arthropathy described in Group A, but are, on the whole, less marked.

It is exceedingly important to note that with the possible exception of Case 39, none of the cases in groups B, C and D gave any symptoms or showed any signs of changes in the joints or long bones, and yet twelve of these were shown by radiographic examination to have periosteal new bone formation. This bone proliferation seen in these twelve cases is of exactly the same type and general distribution as in the five cases in Group A. As in these cases of Group A, and of osteo-arthropathy in general, this hypertrophy was confined to the long bones in the forearms and lower legs, usually in their distal portions, and in a few instances the long bones of the hands and feet. From the history in Case 39 it seems certain that the clubbing of the fingers had existed for many years, while the slight symptoms in the joints were of but a few months' duration; in other words, this appears to be a case of hippocratic fingers which subsequently developed the lesions in the long bones characteristic of osteo-arthropathy. Since roentgenograms were not made previously, actual proof is lacking that this case began as one of simple clubbing and later evolved proliferation in the long bones; yet the previous history is so definite that such a sequence can hardly be doubted.

The question has very naturally been asked, if clubbed fingers is but an early stage of hypertrophic osteo-arthropathy, why has not the transition from the former to the latter been observed? A satisfactory answer is, I believe, found in the results of the examination of the thirty-nine cases recorded above. Although with the possible exception of Case 39, none showed any changes whatsoever in the joints or long bones of the limbs, systematic radiographic examination revealed the presence of typical early lesions of osteo-arthropathy in one or more of the long bones. Were the primary disease to be progressive, it can hardly be doubted, I believe, that these twelve cases would have shown more or less progressive lesions in the long bones and that at least some of the remaining twenty-seven cases would also later have developed

such lesions. The clinical experience of many observers indicates positively that while, as is well known, the clubbing in the fingers secondary to various conditions frequently appears quickly, the development of osteo-arthropathy seldom occurs earlier than at least three or four years after the appearance of the primary disease. The final test would consist in the Roentgen-ray examinations of a series of cases of early clubbing of the fingers occurring with such chronic progressive diseases as pulmonary tuberculosis and bronchiectasis, and subsequently for a period of years. So far as I am aware, no such studies have ever been made. Clinical evidence at least indicates that such is the sequence of events in a considerable number of cases of hypertrophic osteo-arthropathy in which the clubbing was noted for a long time previous to the appearance of symptoms and signs in the joints and long bones of the legs and arms.

Several authors have denied the identity of the type of clubbing in hippocratic fingers and osteo-arthropathy and have attempted to define the differences. It is undoubtedly true that the most marked types of clubbing occur in the well-developed cases of osteo-arthropathy. The finger-ends are more bulbous and the nails usually thicker, more striated and with a greater convexity. I have recently studied a large number of cases of hippocratic fingers occurring with phthisis and other conditions and have compared them with the clubbing in the five cases in Group A. I have been unable to satisfy myself of any differences except such as are to be explained on the basis of the difference in stage of development of the condition; in other words, in my experience the striking changes in the finger-ends in cases of hypertrophic osteo-arthropathy are strictly identical with those seen in hippocratic fingers, except that they represent a more accentuated form. In the rapidly developing type seen with empyema, for example, the swelling of the soft parts is extreme, the nail bed is deeply injected and swollen and the nails are red; whereas in the more chronic and slowly developing type seen with less virulent primary diseases, the swelling is less marked, the nail-bed is seldom injected and the nails are frequently cyanotic.

Every case of hypertrophic osteo-arthropathy so far recorded has shown well-developed clubbing of the fingers and toes, and it is regarded as an absolutely constant sign of the disease.

Finally, it is important to compare the primary diseases with which hippocratic fingers and hypertrophic osteo-arthropathy are associated. A comparison of the primary diseases in the thirty-nine cases of hippocratic fingers given in Table 2, with the primary diseases in a hundred and thirty-nine cases of osteo-arthropathy in the literature and given in Table 1, shows, in many respects, such a close correspondence

as to be very significant. As is perhaps to be expected, there is a considerably greater preponderance of pulmonary tuberculosis in Table 2. The correspondence between the pulmonary diseases, taken as a whole in the two tables is very striking, however, being 72 per cent. of the total in Table 2 and 78 per cent. in Table 1. The individual diseases of the respiratory tract in Table 2 are naturally fewer in number because of the small total of cases, but are seen to be the diseases of the respiratory tract which predominate in Table 1. None is found in Table 2 which does not also occur in Table 1. The percentage of cases of osteo-arthropathy occurring with bronchiectasis is more than twice that of hippocratic fingers occurring with the same condition, whereas pulmonary tuberculosis and cardiac disease are far more common as the associated primary disease in the latter than in the former. It appears then as a result of this comparison that hypertrophic osteo-arthropathy and hippocratic fingers develop secondarily to the same general group of diseases.

Considering the facts then, first, that clubbing of the fingers always occurs in hypertrophic osteo-arthropathy, second, that this clubbing is identical with that found in hippocratic fingers except perhaps in the degree of development, third, that hippocratic fingers and osteo-arthropathy are associated with the same general group of diseases, and fourth, that twelve of the series of thirty-nine cases of simple clubbing examined by the Roentgen ray showed osseous changes in certain of the long bones of precisely the same type as found in osteo-arthropathy, it follows that the two conditions should be regarded as but different stages of the same disease.

#### CONCLUSIONS

1. The evidence is overwhelming that hypertrophic osteo-arthropathy is always a secondary disease.

2. Among the primary diseases, pulmonary tuberculosis is probably the most important though rarely inducing the extreme degree of bone and joint changes seen with bronchiectasis.

3. There is a very definite correspondence between the characteristic clinical course of the disease and the process in the bones. During the periods of exacerbation in the primary disease, the pain, tenderness and swelling in the soft parts are not only increased, but the process in the bones is also more active. On the other hand, during the quiescent periods associated with cure or relief of the condition responsible for the bone and joint changes, the process in the bones is stationary and in rare instances actual resorption takes place.

4. The new subperiosteal bone, which is at first sharply marked off from the old shaft, later becomes (usually after a period of some

years) a more compact, dense layer, closely fused with the underlying old bone.

5. In the late stages of the most progressive type of cases there is evidence of wide-spread haliteresis in the affected long bones.

6. Occasionally the process in the bones and joints once established may progress even after actual cure of the primary disease.

7. The ungual phalanges as a rule show proliferative changes. They consist mainly in an irregular burr-like expansion of the distal half. More rarely small osteophytes are found at the proximal ends near the line of the joint cartilage.

8. The epiphyses of the affected long bones are to some extent always involved, but the new osseous tissue is much more irregular in outline and the ossification is less complete.

9. The proliferation in the long bones in advanced cases is more general than has been recognized, often affecting nearly the entire skeleton.

10. Changes in the joints are a constant and important feature of the disease. While the early changes are confined largely to the peri-articular tissues, in the later stages, erosion of the cartilage, lipping about the joint, and even a moderate degree of ankylosis are common lesions.

11. A considerable percentage of cases of so-called hippocratic fingers show by means of skiagrams early proliferative changes in the periosteum of some of the long bones of the forearms and lower legs of exactly the same type as seen in hypertrophic osteo-arthritis.

12. Simple clubbing of the fingers and secondary hypertrophic osteo-arthritis should be considered as identical, the former representing an early stage of the latter.

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## CHRONIC ULCERATIVE COLITIS WITH POLYPS

A CONSIDERATION OF THE SO-CALLED COLITIS POLYPOSA (VIRCHOW)\*

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The finding of excrescences and polypoid projections of the mucosa in various parts of the alimentary tract is a comparatively frequent occurrence in the post-mortem room. The association of these with inflammation of the intestines, or at least a clinical history of dysentery, while not so frequent, has, nevertheless, been noted and described in the literature for a considerable time.

In 1721 Menzel<sup>1</sup> described a case in which there was a general inflammation of the intestinal tract and in the colon there were a number of wart-like excrescences. He presents with his report a crude etching of about 7 inches of the colon (Fig. 1). On it there are fifteen polypoid projections. The specimen was removed from a soldier who died of chronic dysentery.

In 1832 Wagner<sup>2</sup> in his description of the manner of healing of dysenteric ulcers noted that sometimes on the margins of the scars and on the healed surface of the smooth cicatrix of the healed ulcers tiny polypoid excrescences were found.

In 1839 Rokitsansky<sup>3</sup> confirmed this observation of Wagner's and added that these small excrescences had their origin from islands of the mucous membrane that remained after the ulcerative process had ceased. He, moreover, does not limit the size of the projections. Later,<sup>4</sup> in describing the process of cicatrization of follicular and other ulcers of the colon he described the formation of polypoid growths from the ragged margins of ulcers.

Other systematic writers on pathological anatomy of this period, as Bock<sup>5</sup> among the German, Habershon,<sup>6</sup> Wilkes and Moxon<sup>7</sup> among the

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1. Menzel: *Acta Medicorum Berlinensium*, 1721, ix, 78.

2. Wagner: *Med. Jahrb. d. k. k. ost. Staates*, 1832, xi, 274.

3. Rokitsansky: *Med. Jahrb. d. k. k. ost. Staates*, 1939, xxix, 88; also a *Manual of Pathological Anatomy*, London, 1849, ii, 86.

4. Rokitsansky: *Lehrbuch der path. Anatomie*, Ed. 3, revised, Wien., 1861, iii, 209.

5. Bock: *Lehrbuch der path. Anatomie*, Ed. 4, Leipsic, 1864, p. 420.

6. Habershon: *Diseases of the Abdomen*, Ed. 2, London, 1862, p. 384.

7. Wilkes and Moxon: *Lectures on Pathological Anatomy*, Ed. 2, London, 1875, p. 416.

English, copied Rokitsansky's descriptions, but added no specific observations.

In 1861 Lebert<sup>8</sup> reported the case of a woman, 32 years of age, who had suffered for years from an obstinate diarrhea. At section the mucous membrane of the colon was found beset with hundreds of little polypi, varying in size from a lentil to a bean, some pedunculated, others sessile. He described these polyps as consisting of fibrous tissue containing ramifying blood-vessels, but no glands. Glandular tubules were, however, to be found surrounding the base of the polyps. These tubules appeared normal.

In the same year Luschka<sup>9</sup> described a colon containing on its mucosa thousands of polyps. These varied in size from a hemp-seed to a bean and covered the mucosa from the ileo-cecal valve to the anus. On microscopic examination these polyps were found to consist of glands resembling the glands of Lieberkühn, except that they were longer, many of them more or less branched, and some of them dilated

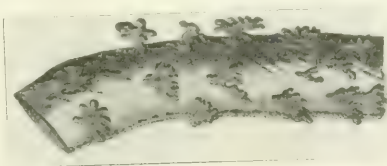


Fig. 1.—A photograph of the etching accompanying Menzel's report. If we compare this with the photograph of the colon from our first case, Figure 3, remembering that the dark areas in both pictures are the ragged tags of mucosa and submucosa, we see that the condition in the two colons must have been practically identical.

into cyst-like spaces. The mucous membrane between the glands was not markedly changed. The patient was a woman 30 years of age. She had for years suffered from a bloody diarrhea.

These last two cases, together with Menzel's, Virchow<sup>10</sup> has given as examples of a condition of the colon which he has called colitis polyposa. To these he has added one case. It was that of a boy 15 years of age who had died of dysentery. The polyps in this case were of the nature of vesicular, fluctuating prominences (Fig. 2). Many of them had scattered over their surfaces small openings from which gelatinous material protruded and could be expressed. Similar material was to be found in the mucosa between the polyps. On microscopic examination these vesicles were found to be dilated crypts of

8. Lebert: *Traité d'anatomie path.*, Paris, 1861, ii, 316

9. Luschka: *Virchow's Arch. f. path. Anat.*, 1861, xx, 133

10. Virchow: *Die krankhaften Geschwülste*, Berlin, 1863, i, 243.

Lieberkühn filled with mucous material. To this condition Virchow gave the name *colitis polyposa cystica*.

In 1881 Woodward,<sup>11</sup> the author of the "Medical and Surgical History of the War of the Rebellion," described two specimens from a colon that was sent to the Museum of the Surgeon General's Office for preservation. The patient was a woman aged 44, who for seven months before death was afflicted with a severe bloody diarrhea. At autopsy the ileum for 4 inches above the ileocecal valve and the colon for its whole length appeared ulcerated and inflamed. In the lower part of the transverse colon there were to be seen single follicular ulcers. These became larger and more numerous in the upper part of the descending colon, till a point was reached at which the whole mucosa was occupied by a single ulcer on the base of which there were numerous islands of thickened and puckered, undestroyed mucous

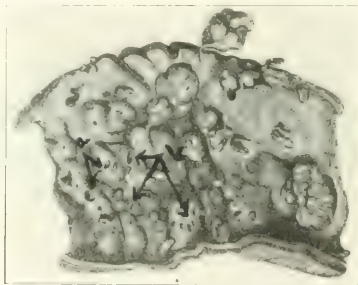


Fig. 2.—A copy of a portion of the colon from Virchow's case of *colitis polyposa cystica*. At "a" and "b" are to be seen open spaces. This suggests that secretions had accumulated in some of the spaces till they ruptured, which would represent a stage farther in this process than we have described.

membrane. The whole mucous surface of the lower portion of the descending colon was occupied by a single ulcer, projecting from the base of which were thirteen polypoid excrescences, some measuring as much as 14 mm. in length and 4 mm. in diameter. Some of the projections were more or less branched, but attached by a single pedicle like a genuine polyp; others were attached by double pedicles.

On microscopical examination the polyps were found to be composed of a central mass of connective tissue and a peripheral border of mucous membrane in a condition like that commonly found in chronic inflammation of the colon. The mucous membrane extended over the surface of the excrescence and its pedicle as far as its base, but was

11. Woodward: *Am. Jour. Med. Sc.*, 1881, lxxxi, new series, p. 142.

absent from the surrounding flat surface of the intestine between the adjacent polyps. The intervening surface was composed of a vascular granulating tissue containing everywhere a large number of lymphoid cells. The glands of Lieberkühn over some of the polyps exhibited active hyperplasia.

The first case of this condition that came under our observation was necropsied at the Cleveland City Hospital about ten years ago. The patient was a woman about 36 years of age. About six months before entering the hospital she had given birth to a normal child. For a considerable time before admission she had been afflicted with a more or less severe diarrhea. Three months before admission this diarrhea had become a dysentery of a very annoying and exhausting character. She was in the hospital only a few weeks when death ensued, apparently from inanition and exhaustion.

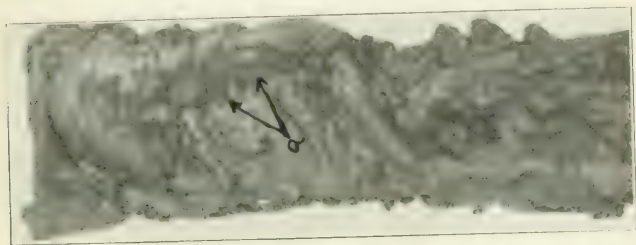


Fig. 3.—A portion of the colon from our first case. The ragged tags of mucosa and submucosa, as seen at "a," are the darker areas. The specimen having been preserved in alcohol had so faded that there was little contrast between the parts.

At the post-mortem examination the only lesion of importance found was in the colon. Here the entire mucous membrane from the ileocecal valve to the rectum was uniformly deeply ulcerated and existed as tags and localized islands (Fig. 3). The wall of the colon was moderately and generally thickened. In microscopic sections it was seen that the ulceration had extended through the submucosa to the muscularis (Fig. 4). The muscularis remained exposed and naked. Near its mucosal surface and extending into it there were numerous islands and columns of lymphocytes and polymorphonuclear leukocytes. There were also scattered eosinophils and plasma cells. The pedicle of the ragged tag of mucosa was composed of swollen and edematous submucosal tissue. In it were a number of blood-vessels, clusters and columns of lymphocytes and polymorphonuclear leukocytes with here and there scattered single eosinophils and plasma cells. The ragged tags were made up of mucosa and a portion of the attached

submucosa. The submucosal portion was everywhere infiltrated with leukocytes of the same character as those noted in the muscularis and pedicle. Large numbers of leukocytes were also seen in the mucosa between the tubules. The glands of Lieberkühn were everywhere more or less intact and there was no marked increase in the connective tissue between them. In certain places there was deposited between the tubules a brownish substance arranged in cell-like masses and in fine granular droplets. The peritoneum was slightly thickened and infiltrated with small round cells.

The following, our second observation, was more recent:

*Patient.*—A white man, aged 40, an American, an elevator man by occupation, was admitted to the Cleveland City Hospital July 26, 1913.

*History.*—His family history and personal history were unimportant. His present illness began with frequent stools two months before admission to the



Fig. 4.—A very low-power microscopic view of one of the tags of preserved mucosa and submucosa from our first case. It is to be noted here that there are no cystic spaces and the mucosa that remains is comparatively normal.

hospital. In spite of medical attention these had persisted and had recently been associated with great loss of weight and strength.

*Physical Examination.*—The patient was a well-developed but poorly nourished man. The skin was anemic, pale, yellow and dry. There were occasional râles to be heard over the chest and a soft systolic murmur along the left border of the sternum. No palpable masses were to be felt over the abdomen. On rectal examination a finger's length up the rectum a hard raised ring could be felt and all around it there were elevated masses. Blood and mucus came away readily with the finger as it was withdrawn. The blood-count on admission was, red blood cells, 4,048,000; white blood-cells, 6,600; hemoglobin, 50 per cent. Differential count, polymorphonuclear neutrophils, 63.5 per cent.; small mononuclears, 18.5 per cent.; large mononuclears, 7 per cent.; transitionals, 5 per cent.; eosinophils, 0.5 per cent.; mast cells, 0.5 per cent. There was fairly marked anisocytosis and poikilocytosis. A specimen of feces



examined on admission was of a reddish-brown color and of very foul odor. It gave a positive test for bile. Microscopically numerous red blood-cells were to be seen but no amebas parasites, or ova of parasites. The Wassermann reaction was negative. Examination of the urine gave, on admission, a faint trace of albumin. This soon disappeared, and thereafter the urine was negative for albumin, sugar and casts.

*Course.*—The patient was in the hospital a little over three months and three weeks. During this period the temperature was quite variable but never above 101. Generally it was normal or subnormal. The number of stools varied from one to four per day. The patient died in the hospital.

*Clinical Diagnosis.*—Carcinoma of rectum.

*Necropsy.*—Performed about six hours after death. Excepting a moderate parenchymatous degeneration of the heart muscle, liver and kidneys, and a peripheral fatty degeneration of the liver lobules, there were no lesions of importance to be noted outside of the alimentary tract.

The stomach, duodenum and jejunum presented nothing markedly abnormal.



\* Fig. 5.—A cluster of polyps from our second case. At *a* and *b* are to be seen numerous small islands of mucosa and of submucosa.

The mucosa of the lower two-thirds of the ileum was injected; edematous, and its surface covered with a thin, grayish layer of exudate. At irregular intervals small areas of marked injection, as of beginning ulcers, were to be noted. In the lower portion of the ileum, near the ileocecal valve, and in the cecum there were single ulcers. These ulcers were of all sizes from a millimeter to a centimeter in diameter. The small ulcers were of a "punched-out" character and extended only through the mucous membrane. The larger ulcers were very irregular, with ragged margins and floor, and extended deeper into the intestinal wall. On the base of several of the largest ulcers there were attached islands and tags of mucosa and submucosa.

The appendix appeared normal and not to have been at all affected by the inflammatory process involving the cecum and ileum.

The wall of the colon was generally and moderately thickened, rather fibrous and stiffly flexible, though in some places it had been so eroded as to be thinner than normal. The intestine was generally contracted and its lumen narrowed. The mucosa of the ascending and transverse portion was covered

with a thin layer of grayish exudate. It was moderately injected and, over irregular areas, eroded to varying depths. Over the eroded areas were to be seen islands of deeply injected mucosa. Many of the small tufts of mucosa were attached by slender pedicles of submucosa and were easily removed by passing the finger over the surface. In the descending colon the mucosa was likewise injected and eroded. At a point about 8 cm. above the sigmoid flexure there were to be seen a few short polypous projections. These projections measured from 2 to 3 mm. in diameter. They were stubby and attached by a relatively thick pedicle. About the sigmoid flexures there was a cluster of fairly large and long polypous masses. One of these masses in particular had a long slender pedicle and a clubbed termination. It measured about 2.5 cm. in total length and the clubbed extremity 4 mm. in diameter at its widest part.

From the sigmoid flexure to about 12 cm. above the external sphincter of the anus polypous projections were more numerous and of various sizes and shapes. Some of the polyps were small sessile projections, measuring from 1 to 2 mm. in height and in diameter; others were irregular, 0.5 to 1.5 cm. in length and in diameter, attached by short slender pedicles—some of the



Fig. 6.—A copy of the drawing of a microscopic section of one of the polyps from Woodward's case. The central mass of connective tissue and the surrounding layer of preserved mucosa is well shown.

pedicles appearing so slender as to be scarcely strong enough to support the nodule on their ends (Fig. 5). In all, there were about forty polypous projections.

*Microscopic Examination.*—In microscopic sections of the lower portion of the ileum the mucous membrane was found to be swollen and edematous. Its surface was covered with a layer of mucus and detritus in which large numbers of leukocytes and glandular desquamated cells were to be seen. The connective tissue between the crypts and glands of Lieberkühn was moderately increased and infiltrated with polymorphonuclear leukocytes, lymphocytes and plasma cells. The blood-vessels were dilated and filled with blood. The submucosa and muscular layer were likewise swollen, edematous and infiltrated with leukocytes. The peritoneal layer was slightly swollen and infiltrated with leukocytes, but there was no exudate on its surface.

In sections of the single ulcers in the lower portion of the ileum and in the cecum there were seen to be areas of necrosis and ulceration, in some places extending no deeper than the mucosa; in other places, however, particularly in association with the larger ulcers, the necrosis extended through the sub-

mucosa to the muscularis. The margins of the ulcers were swollen, edematous and infiltrated with fibroblasts, large numbers of lymphocytes, polymorphonuclear leukocytes, eosinophils and plasma cells. Some of the margins were sloping and fairly smooth; others were deeply undermined, irregular and ragged. The floor of the ulcers, particularly the large ulcers, was, for the most part, smooth but irregular in outline. There were small elevations on the floor of many of them. These elevations were quite vascular. Some of them were covered with mucous glands; others contained only the fundi of the glands, while others were simple vascular tufts without covering.

The mucous surface of the colon everywhere presented the picture of a chronic inflammatory and ulcerative process with here and there areas and islands of granulation tissue. The surface was covered with a layer of necrotic tissue cells which extended to a variable depth from a few micromillimeters below the surface of the mucosa to several micromillimeters into the submucosa, even to the muscular layer. Beneath the layer of necrotic cells the glandular tubules, where present, were spread far apart by the proliferation of fibroblasts and the infiltration of lymphocytes and polymorphonuclear leukocytes, eosinophils and plasma cells. In most places only the bases of the crypts of Lieberkühn remained. In some places these had been overgrown by the



Fig. 7.—A very low power photomicrograph of a section of one of the polyps from our second case to show the dilated cystic spaces in the mucous layer. The dark line across the top represents a fold in the section.

fibroblasts and the accumulation of secretions had caused them to become dilated and to appear as small cysts. The blood-vessels and capillaries were dilated and congested. Scattered areas of hemorrhage were to be seen on the surface. The submucosa, where not eroded, was generally thickened and fibrous. Infiltrating it were a number of scattered areas of leukocytes, eosinophils and plasma cells. The solitary follicles were small and irregular in size and distribution. The muscular layers were moderately infiltrated with lymphocytes, leukocytes, eosinophils and plasma cells. The peritoneum appeared slightly thickened.

The sessile projections and polyps, noted in the descending colon and rectum, microscopically presented the same appearance as that described and pictured by Woodward in the case he described (Fig. 6). There was a central mass of connective tissue which formed the base and support of the polyp. The central connective tissue mass was surrounded by an irregular, rather thick, layer of glandular acini and tubules. The connective tissue extended between the tubules and had in places contracted and occluded them, causing a retention of secretions of the glands and cyst-like dilatations (Fig. 7). The structures were quite vascular and everywhere infiltrated with lymphocytes, polymorphonuclear leukocytes, eosinophils, plasma cells and large epithelioid cells

The mucosae around the bases and pedicles were for the most part absent, or represented only by scattered fundi of crypts imbedded in fibrous tissue. They were very vascular. The blood-vessels were dilated and engorged with blood. Many of the smaller tufts were made up entirely of collections of budding blood-vessels, fibroblasts, and leukocytes without mucous crypts or glands.

The islands and tags of mucosa and submucosa that had been the source of the polyp formation appeared to depend for their preservation on the blood-vascular arrangement; for it was to be noted that the polyps in the rectum were situated along the side of the intestinal wall, while higher up and in the colon the polyps were situated along the line of attachment of the mesentery, an arrangement that coincides with the blood-supply of the parts. The blood-supply of these small and localized areas appeared to have been sufficient to withstand the destructive action of the inflammatory process, so that necrosis did not take place. The coincident increased blood-supply did, however, produce active hyperplasia of the mucous glands and the submucous connective tissue, with consequent polyp-like formations, as described by Rokitsansky. The increased and proliferated fibrous tissue on contracting had caused an occlusion of many of the tubules and retentions of their secretions had caused cyst-like formations, as described by Virchow. Probably, as Virchow has suggested, the formation and lengthening of the pedicles of the polyps had been aided by the active peristalsis and the passing of the feces over the surface of the polyp. Our second specimen, like Luschka's, was not cystic, but cyst-like spaces were present over the mucous surface of the colon between the polyps and over the surfaces of the polyps (Fig. 7).

It appears very probable that the two cases which we have here presented represent, respectively, a very early and a comparatively late stage in this particular condition of the colon designated by Virchow as colitis polyposa. If so, they, with the cases reported in the literature, aid us materially in working out the natural pathological history of the lesions of this affection and of ulcers of the alimentary tract.

There appears in the beginning of this disease to be a general colitis, producing a number of local undermining ulcers similar to those found in our second case in the cecum and in the lower portion of the ileum, near the ileocecal valve. Clinically, there is associated with the lesions at this stage a moderate diarrhea. The ulcers tend to increase in number and in size till nearly the whole mucous surface of the colon is involved. Clinically, during this period there is an increase in the number and a change in the character of the stools. The ulcers as they increase in size fuse and form large irregular ulcerated areas, similar to those presented in our first specimen (Fig. 3). The ulcerative process, though severe and chronic, is of such a character that portions

of the mucosa and submucosa adjacent to and supplied, apparently, by the primary arterial branches is preserved. These portions of the mucosa and submucosa remain as ragged tags scattered over the surface of the colon. As the process ameliorates and healing begins the irregular margins of these tags become smoothed off and remain as rounded sessile elevations or as polypoid projections of the mucous surface. The portions of the mucosa that remain in these areas regenerate over the surface, around the base or pedicle and, if conditions remain favorable, ultimately, over the barren and denuded submucosa and together with submucosa over the muscular layer. The mucosa may thus be completely restored, and, with its numerous scattered polypous projections, present a perfect picture of colitis polyposa. Coincident with the process of healing, and later, the proliferated fibroblasts begin to contract, as in the cicatrization of a wound. This leads to an occlusion of the orifices of certain of the tubules situated in the polyps and over the mucosa between the polyps. There is then an accumulation of secretions in these occluded tubules with the ultimate formation of retention cysts. These of course increase in size as long as there are secreting cells in their walls, and as there are a greater number of tubules over the surface of the polyp than over the surface of the mucosa, the polyp may appear as a collection of small cysts. It is probably in this manner, as before stated, that the condition which Virchow has designated as colitis polyposa cystica is brought about. It is the end stage of colitis polyposa.

# OBSERVATIONS ON THE USE OF THE ABDERHALDEN REACTION WITH NORMAL AND PATH- OLOGICAL HUMAN SERUMS\*

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The material of this paper is arranged in the following order:

1. Negative reactions with testicular substrate and male dementia praecox serum.

2. A comparison between the blood-serum of normal persons and those suffering with general paralysis of the insane as regards proteolytic action on brain substrates at various stages of washing.

3. Proteolysis of substances precipitated from the water used for washing various organs in the course of preparing substrates.

4. Comparison of the proteolysis of emulsions, prepared by concentrating the washings from brain substrate, by serum from general paralysis and normal persons.

In a previous communication<sup>1</sup> we proved, first, that the serums of normal animals contain ferments capable of giving positive Abderhalden reactions with substrates prepared from many body tissues, and second, that the substance (or substances) which gives the reaction may be removed from the substrates if the washing<sup>2</sup> with acidified water is continued long enough. This work was done on dogs and cats. The results to be reported here were obtained with human serums and substrates.

First, it was demonstrated that normal human blood serum contains ferments capable of digesting brain tissue substrate at a certain stage in the process of washing, when it no longer gives any ninhydrin reaction without previous lysis. It was also demonstrated that the washings contain a substance capable of digestion by normal serum. As these results will be used for the demonstration of certain other points in comparison with pathologic serums, the tabulation for the moment will be postponed.

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\* From the laboratory of the Illinois State Psychopathic Institute.

\* Read before the Mississippi Valley Medical Association, Oct. 29, 1914.

1. Ross, E. L., and Singer, H. D.: A Point to be Considered in the Use of the Abderhalden Reaction, *THE ARCHIVES INT. MED.*, 1914, xiv, 552.

2. It should be stated that this refers to the washing by boiling after the tissues have been thoroughly freed from blood by washing in cold water, as recommended by Abderhalden.



REACTIONS BETWEEN DEMENTIA PRAECOX SERUM AND SEX-GLAND  
SUBSTRATE

As our work demands a special interest in the problems of psychiatry we have performed a series of tests on the digestion of substrates prepared from testes with the serum of male patients presenting a dementia praecox picture. The available supply of this tissue was necessarily small, hence all was composited and it was then washed twenty times. The series of blood-serums employed for testing with this material comprised seventeen cases of undoubted dementia praecox type, and all, with one exception, gave an entirely negative result. One serum was recorded as doubtful, there being a mere suspicion of a blue color on boiling with ninhydrin. It thus seemed clear that sufficient washing of the substrate will cause a negative reaction between the blood-serum of these individuals and testicular tissue.

It is therefore justifiable to insist, as was done in our previous communication<sup>1</sup> that a positive Abderhalden reaction with sex-gland means nothing at all unless it is demonstrated to be stronger than that obtained with a sample of the identical (not merely similar) substrate and a series of normal serums.

REACTIONS OF GENERAL PARALYTIC AND NORMAL SERUMS WITH BRAIN  
SUBSTRATES

Sex-glands are so small that it is impossible, without a prolonged wait, to use them for a series of studies. In paresis, however, we have an excellent example of a disease in which an organ, the brain, is undergoing destruction and alteration from its normal structure and composition. According to Abderhalden's theory of the development of protective ferments, the serums of paretics should certainly contain enzymes capable of digesting brain protein. Therefore, as these materials were readily obtainable, it was decided to work with brain substrate and paretic serums.

In the light of our previous results, the washing of the brain tissue was made a prominent factor in the investigation. Each brain was washed twelve to fourteen times. At different stages of this washing quantities of the tissue were taken out and saved as an individual substrate. Thus, from each brain, three or four substrates were prepared.

*Source of Material.*—Since it has not yet been determined whether it is permissible to use pathological material for substrates, it seems well to specify the source of the material employed.

*Brain 1* was obtained five hours after death, from a white man 24 years of age, who died seven hours after an injury to the head which had given rise to a hemorrhage at the base of the brain in the region of the right carotid artery. From the history obtained, this

man had always been healthy, did not take alcoholic beverages and had had no venereal infection. No evidence of disease was found anywhere in the body either macroscopically or microscopically.

*Brain 2* was removed twelve hours after death, from the body of a white man 42 years of age. This man had been epileptic for thirty years and was considerably demented. Death took place in a condition of status epilepticus and the autopsy revealed engorgement of

TABLE 1.—ABDERHALDEN TESTS WITH SERUM OF PARETICS AND BRAIN PROTEIN

Donor of Serum	Source of Substrate	Results at Different Stages of Washing. Substrate Boiled with Acidified Water								
		2 Times	3 Times	5 Times	8 Times	10 Times	11 Times	13 Times	14 Times	15 Times
A. C. ....	Brain 1	....	++	....	+	....	....	—	....	....
A. B. ....	Brain 1	....	++	....	+	....	....	—	....	....
L. C. ....	Brain 1	....	++	....	+(?)	....	....	—	....	....
C. S. ....	Brain 1	....	+	....	—	....	....	—	....	....
E. M. ....	Brain 1	....	+	....	—	....	....	—	....	....
D. M. ....	Brain 1	....	+	....	—	....	....	—	....	....
A. C. ....	Brain 2	....	....	....	....	....	....	....	....	—
A. B. ....	Brain 2	....	....	....	....	....	....	....	....	—
L. C. ....	Brain 2	....	....	....	....	....	....	....	....	—
F. F. ....	Brain 2	+++	....	++	....	+	....	....	....	—
W. B. ....	Brain 2	+++	....	++	....	—	....	....	....	—
E. J. ....	Brain 2	....	....	++	....	—	....	....	....	—
J. H. ....	Brain 3	+++	....	++	+	....	+	....	—	....
W. R. ....	Brain 3	++	....	+	+(f)	....	+	....	—	....
W. L. ....	Brain 3	++	....	++	+	....	—	....	—	....
L. C. ....	Brain 3	+	....	+	—	....	—	....	—	....
T. G. ....	Brain 3	+	....	+	—	....	—	....	—	....
A. B. ....	Brain 3	+	....	—	—	....	—	....	—	....
A. C. ....	Brain 3	+	....	—	—	....	—	....	—	....
E. J. ....	Brain 3	+	....	—	—	....	—	....	—	....
Total positives possible		30	18	33	42	9	24	18	24	18
Actual positives obtained		18	9	13	6	1	2	0	0	0
Percentage of positives		60.0	50.0	39.4	14.3	11.1	8.3	0.0	0.0	0.0

TABLE 2.—ABDERHALDEN TEST WITH SERUM OF NORMAL PERSONS AND BRAIN PROTEIN

Donor of Serum	Source of Substrate	Results at Different Stages of Washing. Substrate Boiled with Acidified Water								
		2 Times	3 Times	5 Times	8 Times	10 Times	11 Times	13 Times	14 Times	15 Times
T. B. ....	Brain 1	....	+(?)	....	—	....	....	—	....	....
E. R. ....	Brain 1	....	—	....	—	....	....	—	....	....
R. M. ....	Brain 1	....	—	....	—	....	....	—	....	....
H. S. ....	Brain 1	....	—	....	—	....	....	—	....	....
E. R. ....	Brain 2	++	....	....	....	....	....	....	....	—
T. B. ....	Brain 2	++	....	—	....	—	....	....	....	—
R. M. ....	Brain 2	++	....	—	....	—	....	....	....	—
H. S. ....	Brain 2	+++	....	—	....	—	....	....	....	—
H. S. ....	Brain 3	+	....	—	—	....	—	....	—	....
C. N. ....	Brain 3	+	....	—	—	....	—	....	—	....
E. F. ....	Brain 3	+	....	—	—	....	—	....	—	....
E. R. ....	Brain 3	+	....	—	—	....	—	....	—	....
Total positives possible		24	12	21	24	9	12	12	12	12
Actual positives obtained.....		13	1	0	0	0	0	0	0	0
Percentage of positives		54.2	8.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0

cerebral vessels, an old hemorrhagic cyst in the left hippocampus, healed tuberculosis of lungs and cholelithiasis with chronic inflammation of the liver and splenic capsules.

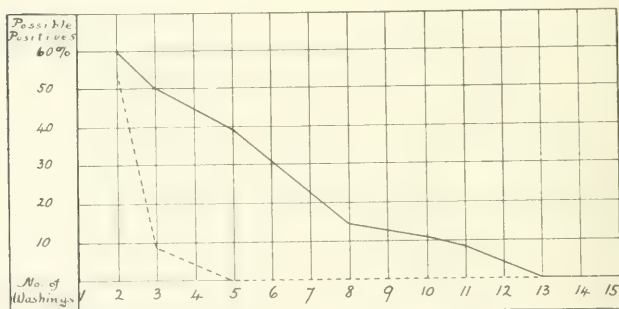
*Brain 3*, removed twenty hours after death from the body of a white woman, aged 61. The woman had presented a picture of a paranoid type of dementia praecox for more than twenty years. Death resulted from a subacute ulcerative colitis with an abscess in the left lung. There was much fatty degeneration of the myocardium and liver and some cloudy exudate beneath the pia mater.

Brain 1 may be considered as an ideal specimen for the purpose, whereas Brains 2 and 3 are both of questionable value. Nevertheless, the results in all three are so similar that it has been deemed justifiable to combine them for the purpose of drawing conclusions.

A series of tests with paretic and normal serums was made on each brain series. The results are given in Tables 1 and 2.

The curves shown in the chart are constructed from the data of Tables 1 and 2. The horizontal distances represent the number of washings while the vertical distances indicate the proportion, in percentage, of the actual number of positives obtained to the number possible, allowing + + + as a complete reaction.

It is evident from these results that the ferment activity of the serum of paretics differs from that of normal persons. Even with the fewest number of washings the substrate was slightly less digested by normal serums. The third washing seemed to have caused the greatest difference in the digestibility of the tissue by the two classes of serum. No digestion of the brain occurred with normal serum after it had been washed five times, while there was considerable digestion with paretic serum till the thirteenth washing was reached. This is capable of various explanations.



Proteolysis of brain substrates at different stages of washing by serums from normal persons and cases of general paralysis. General paralysis serum, solid line; normal serum, broken line.

The first possibility which occurred to us was that the substrate might contain originally at least two classes of proteins, one easily washed out with acidified water, the other requiring more prolonged washing. If, then, the serum of paretics contained two kinds of ferment, one of which was common to all human blood-serum and caused lysis of the easily removable protein, while the other was specific in the sense that it was produced in response to the absorption of dead brain tissue resulting from the disease, paresis, and which acted on that class of proteins less easily washed out, the main facts established by these tests would be intelligible. Such a view is not out of harmony with Abderhalden's theory of protective ferments, although it brings in other factors not hitherto considered.

This would readily explain the abrupt fall in the curve showing the digestion of brain substrate by normal serums after the second boiling, and would permit an understanding of the digestion of substrates from various organs by normal serums. Nevertheless, it seemed also necessary to consider a simpler explanation, at variance with the more generally accepted views, which is to the effect that there may be in brain substance a class of proteins capable of being washed out by boiling with acidified water and at the same time of being digested by a ferment (or ferments) present in both normal

TABLE 3.—EFFECT OF VARIATIONS IN QUANTITY OF SERUM USED\*

		Results on Brain 1 when Boiled		
Power of Serum	Quantity of Serum, cc.	2 Times	5 Times	8 Times
Parasites				
I. C. ....	0.5	—	..	..
F. G. ....	0.5	—	..	..
A. B. ....	0.5	—	..	..
A. C. ....	0.5	—	..	..
E. J. ....	0.5	—	..	..
I. C. ....	1.0	+	+	..
F. G. ....	1.0	+	..	..
A. B. ....	1.0	+	..	..
A. C. ....	1.0	+	..	..
E. J. ....	1.0	+	—	..
I. C. ....	1.5	+	—	..
F. G. ....	1.5	+++	..	..
A. C. ....	1.5	+++	..	..
E. J. ....	1.5	+++	—	..
Normal				
H. S. ....	1.0	+	—	—
C. N. ....	1.0	+	—	..
A. F. ....	1.0	—	—	..
E. R. ....	1.0	+	..	..
E. R. ....	1.5	++	..	..

\* It should be noted that control tests with substrate alone and with serum alone in similar quantities were used in each instance and showed reactions negative.

and paretic serum, but that the conditions for enzyme activity are more favorable, for some reason, in paretic than in normal serum.

To test this latter hypothesis a series of reactions was made on brain substrates with varying amounts of serum. The results are given in Table 3.

From these results it is obvious that the quantity of serum used materially affects the degree of proteolysis which occurs, and hence that it is permissible to consider quantity as well as quality of ferment as a factor in determining the results of the test.

#### REACTIONS WITH NORMAL SERUMS AND PRECIPITATES FROM WASHINGS OF SUBSTRATES

In a previous paper we showed that a material which gave a positive Abderhalden reaction with normal animal serums could be precipitated with alcohol from the water used for washing in the preparation of animal substrates. Similar preparations were made from human tissues. The results of reactions with these precipitates are given in Table 4.

TABLE 4.—ABDERHALDEN TESTS WITH NORMAL SERUM AND SUBSTANCES PRECIPITATED FROM TISSUE WASHINGS

Donor of Serum	Substrate	Result
H. S. ....	Thyroid preparation.....	+
H. S. ....	Spleen .....	—
H. S. ....	Testes .....	++
H. S. ....	Placenta .....	++
E. R. ....	Suprarenal .....	++
E. R. ....	Brain .....	+
E. R. ....	Liver .....	—
E. R. ....	Kidney .....	++

\* Male.

From Table 4 it will be observed that positive reactions were obtained with precipitates from the washings of all organs tested, with the exception of liver and spleen. It is of especial importance to note that a strong positive was obtained with a normal male serum and the precipitate from placental washings. These results, and especially that with the placental preparation, suggest that there is some one protein (or group of proteins) common to most tissues which is capable of lysis by ferments normally present in the blood-serum.



PROTEOLYSIS OF EMULSIONS OBTAINED FROM WATER USED FOR WASHING  
SUBSTRATES ALREADY NEGATIVE TO NORMAL SERUMS

It will be noticed in Table 2 that no normal serum tested gave a positive reaction with substrate which had been washed five or more times, and in Table 1 that the number and degree of positive reactions with the use of paretic serums gradually diminished as the washing was continued, until they finally disappeared entirely. It thus seemed possible that an examination of the fluid used for washings later than the fifth might throw some light on the relation of the material washed out of the substrate at this stage to the ferments present in normal and paretic serums. For it seems clear that all the protein capable of

TABLE 5.—ABDERHALDEN TEST WITH AN EMULSION PREPARED BY CONCENTRATING THE WATER USED FOR THE FIFTH TO EIGHTH WASHINGS OF BRAIN SUBSTRATE, INCLUSIVE

Donor of Serum	Quantity of Emulsion				
	3 c.c.	1 c.c.	0.5* c.c.	0.2* c.c.	0.1* c.c.
<b>Paretics—</b>					
L. C. ....	+	..	..	..	..
F. G. ....	+++	..	..	..	..
A. C. ....	+++	..	..	..	..
E. J. ....	+++	..	..	..	..
R. M. ....	..	+	—	—	—
E. M. ....	..	++	—	—	—
F. P. ....	..	++	—	—	—
<b>Normals—</b>					
H. S. ....	..	++	++	—	—
H. C. ....	..	+	—	—	—
E. R. ....	..	+	++	—	—

\* The bulk was made up to 1 c.c. by the addition of distilled water.

cleavage by protective enzymes present in blood-serum is gradually removed, and hence that if there be two kinds of such proteins and two kinds of ferment, as in the hypothesis advanced above, those washings made after the substrate has become negative to normal serum, will contain only, or almost alone, the substance more difficult of removal, and, according to the hypothesis, capable of digestion only by a ferment specific for paretic serum. In such case the material precipitated from these later washings should give a negative reaction with normal serum and a positive with paretic serum, or at least the reaction should be more marked with the latter than with the former.

For this purpose the fifth, sixth, seventh and eighth washings were compounded and were concentrated to an emulsion by heating on a steam bath. As nothing was known of the amount of this emulsion to be used for a test, varying amounts were employed with 1 c.c. of serum from both parietic and normal persons. Control tests with emulsion alone and serum alone were negative throughout. The results of the tests are given in Table 5.

These results demonstrate that the material which was washed out, even after the substrate had ceased to give a positive reaction with normal serum, was still as readily digested by normal as by parietic serum, and consequently point strongly to the conclusion that the continued positive reaction with parietic serums is due to some factor which favors enzyme activity in these as compared with normal serums. This might be expressed by saying that the difference is quantitative rather than qualitative.

#### SUMMARY

1. Substrates prepared from certain human tissues contain material which is digested by ferments present in normal human serum.
2. This material can be washed out by boiling repeatedly with slightly acidified water.
3. The water used for washing contains material which can be digested by normal serum ferment.
4. Brain substrate which has been washed until it no longer gives positive reactions with normal serum may still be digested by the serum of general paralytics.
5. The material which undergoes lysis from the action of ferments in the serum of general paralytics can be removed by further washing.
6. The material removed by washing after the substrate has become negative to normal serum is digested by the ferments of normal serum in as great a degree as by that of general paralysis.

#### CONCLUSIONS

The published results of experiments on the lysis of tissue substrates by various pathological serums are of no value in permitting conclusions as to the seat of the lesion.

The difference in ferment activity on brain substrates between the serum from general paralysis and that from normal persons appears to be quantitative rather than qualitative.

## THE FACTORS OF COAGULATION IN PRIMARY PERNICIOUS ANEMIA \*

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Within the past two years it has become more and more possible to study the factors concerned in blood coagulation. The literature of this period has even given promise of an etiological classification of hemorrhagic disease, but developments have not borne out this promise. If we accept the theory of Howell,<sup>1</sup> there are five factors in coagulation — antithrombin, thromboplastin, calcium salts, prothrombin and fibrinogen — which may show variations in disease. Antithrombin, prothrombin, calcium salts and fibrinogen are present in the circulating blood. The prothrombin, however, is held in combination with antithrombin and thus prevented from activation into thrombin by calcium. Without thrombin there can be no coagulation. The presence of thrombin is secured through the fixation or neutralization of antithrombin by thromboplastin. This last substance, thromboplastin, frees the blood of antithrombin; under these conditions calcium at once forms thrombin from prothrombin; thrombin reacts with fibrinogen and gives fibrin.

If, on the other hand, we accept the theory of Morawitz, with which most other theories can be brought into accord, we have four possible factors to consider. The existence of antithrombin is admitted by this investigator, but it is not regarded as an essential part of the process. According to Morawitz, thrombokinase (Howell's thromboplastin) transforms thrombogen — normally circulating in the blood — to prothrombin; prothrombin later is converted into thrombin by calcium salts. Thrombin reacts with fibrinogen and gives fibrin. It is not possible to differentiate thrombogen and prothrombin so that the latter alone represents this factor in our experiments.

### QUANTITATION OF THE COAGULATION FACTORS AND THEIR VARIATIONS IN DISEASE

1. *Antithrombin*.—Howell<sup>2</sup> has given us a rapid method for preparing thrombin. Making use of this thrombin and of a normal salt

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\* From the Peter Bent Brigham Hospital, Boston.

1. Howell, W. H.: The Role of Antithrombin and Thromboplastin (Thromboplastic Substance) in the Coagulation of the Blood, *Am. Jour. Physiol.*, 1911, xxix, 187.

2. Howell, W. H.: Rapid Method of Preparing Thrombin, *Am. Jour. Physiol.*, 1913, xxxii, 264.

solution of dried oxalated plasma, which contains active fibrinogen, he has shown that we may get coagulation in from three to ten minutes. Such a system can be rendered non-coagulable, or coagulation can be greatly delayed by the addition of oxalated plasma which has been heated to 60 C. This prevention of coagulation is ascribed to the antithrombin present normally in the blood, and on this basis one may readily test the antithrombin in different clinical conditions. Our technic for these determinations has been that described by Howell<sup>3</sup> and is illustrated in the protocol which follows. Making use of this method, Howell<sup>3</sup> has shown a diminution of antithrombin in three cases of thrombosis; Whipple<sup>4, 5</sup> an increase in one case of profound septicemia; in a case of typhoid fever with complicating liver disease; in a case of miliary tuberculosis with epistaxis; in a case of generalized thrombosis; in a case of leukemia with purpura; in a case of aplastic anemia with purpura and hemorrhage from the nose and gums. These are diverse conditions, and the method of taking the blood has not been uniform. In many of his determinations Whipple used blood from the heart collected some time after death, and his controls in antithrombin have not been as complete as Howell's present methods seem to us to require. Austin and Pepper<sup>6</sup> found an increase in antithrombin in one case of simple purpura.

2. *Thromboplastin (thrombokinase of Morawitz).*—Thromboplastin can be shown to be present in blood in many ways, but for quantitation there is at present no better method than the platelet count. It must be noted, however, that all the formed elements of the blood have been shown to have thromboplastic properties and that the platelets have also been shown to contain prothrombin,<sup>7</sup> so that by this count we do not accomplish our purpose either completely or exactly. The literature on the platelets is large, and it suffices to say that they have been shown to be increased in pneumonia, post-hemorrhagic anemia, and myeloid leukemia; in short, in diseases leading to multiplication of bone-marrow cells. They are decreased in most cases of pernicious anemia, in lymphatic leukemia, in typhoid and many other fevers, and in purpura hemorrhagica, whether primary or secondary. With the

3. Howell, W. H.: The Condition of the Blood in Hemophilia, Thrombosis and Purpura, *THE ARCHIVES INT. MED.*, 1914, xiii, 76.

4. Whipple, G. H.: Hemorrhagic Disease—Septicemia, Melena Neonatorum and Hepatic Cirrhosis, *THE ARCHIVES INT. MED.*, 1912, ix, 365.

5. Whipple, G. H.: Hemorrhagic Disease. Antithrombin and Prothrombin Factors. *THE ARCHIVES INT. MED.*, 1913, xii, 637.

6. Austin, J. H., and Pepper, O. H. P.: Experimental Observations on the Coagulation of Oxalated Plasma, with a Study of Some Cases of Purpura, *THE ARCHIVES INT. MED.*, 1913, xi, 305.

7. Morawitz, P.: Beiträge zur Kenntniss der Blutgerinnung, *Deutsch. Arch. f. klin. Med.*, 1904, lxxix, 215; Baynes-Jones, S.: The Presence of Prothrombin and Thromboplastin in the Blood Platelets, *Am. Jour. Physiol.*, 1912, xxx, 74.

exception of one observation by Austin and Pepper<sup>6</sup> we know of no cases of hemophilia in which they have been found deficient. Sahli<sup>8</sup> and Morawitz and Lossen<sup>9</sup> ascribe hemophilia to defective formation of thromboplastic material by injured vessel walls. This opinion is arrived at by a process of exclusion of other factors, but not by direct experiment.

3. *Calcium*.—The third factor in the coagulation system, calcium, has not been studied in our series of cases. Wright<sup>10</sup> has advocated the treatment of hemophilia by administration of calcium, and the weight of his advice has led to the indiscriminate use of calcium salts in bleeding conditions. Nolf<sup>11</sup> has absolutely denied calcium diminution in hemophilia, and it appears probable that this factor may be neglected in hemorrhagic disease.

4. *Prothrombin*.—This cannot be determined with entire certainty. If one takes oxalated plasma and to a series of tubes adds dilute calcium chlorid, coagulation will result and the coagulation time will be shortest in the tube which happens to receive the optimum amount of the salt. Howell<sup>3</sup> has held that this is a quantitative test for prothrombin, and making use of it he has shown a great prolongation of coagulation time (on recalcification) in three cases of hemophilia, and he therefore ascribes the disease to a prothrombin deficiency. We believe the test most useful, but think it should be subjected to certain precautions. Lee and Vincent,<sup>12</sup> using human blood, have shown that the time of coagulation of recalcified oxalated plasma varies directly with the length of time of centrifugalization and they have felt that this is due to removal of formed elements. Perfectly clear plasma, the result of prolonged high-speed centrifugalization, clots in forty-five minutes on recalcification; cloudy plasma poorly centrifugalized in fifteen minutes at most. It seems proved, therefore, that the speed of Howell's prothrombin reaction can be modified by centrifugalization, and it is probable that this is due to alterations in the solid content of the plasma. Since each prothrombin test must be controlled by a similar test on normal plasma it becomes of prime importance that the test and control material be similarly treated.

8. Sahli, H.: Ueber das Wesen der Hämophilie, Ztschr. f. klin. Med., 1905, lvi, 264.

9. Morawitz, P., and Lossen, J.: Ueber Hämophilie, Deutsch. Arch. f. klin. Med., 1908, xciv, 110.

10. Wright, A. E.: Remarks on Methods of Increasing and Diminishing the Coagulability of the Blood, with Especial Reference to Their Therapeutic Employment, Brit. Med. Jour., 1894, ii, 57.

11. Nolf, P.: Eine Neue Theorie der Blutgerinnung, Ergebn. d. inn. Med. u. Kinderh., 1913, x, 275.

12. Lee, R. L., and Vincent, Beth: The Coagulation of Normal Human Blood, THE ARCHIVES INT. MED., 1914, xiii, 398.

Without mentioning the use of such precautions, Whipple<sup>4, 5</sup> has reported two cases of melena neonatorum with diminished prothrombin. Addis<sup>13</sup> also believes that a diminution of prothrombin is the cause of hemophilia.

5. *Fibrinogen*.—This remains as the fifth factor in the system. It may be estimated very readily by the heat coagulation method outlined by Whipple and Hurwitz.<sup>14</sup> By a slight modification of this method Whipple<sup>15</sup> has demonstrated an increase in fibrinogen in two cases of lobar pneumonia and in one of acute hemorrhagic colitis, a great decrease in chloroform poisoning, experimental and clinical, a decrease in two cases of cirrhosis of the liver and in five cases of cachexia from varying causes. The same observer reports normal fibrinogen in eclampsia, aplastic anemia and cancer of the liver.

During the past winter we have used the methods outlined above in the following cases:

Purpura .....	5
Spontaneous thrombosis .....	1
Cirrhosis of the liver .....	4
Chronic lymphatic leukemia .....	1
Secondary anemia and sarcoma .....	1
Pernicious anemia .....	7
Total .....	19

Our results in the non-anemic cases may be summarized as follows:

1. Purpura: Platelet count was reduced in two cases. Other factors were normal.

2. Spontaneous Thrombosis: Platelets were not studied. Other factors were normal.

3. Cirrhosis of the Liver: Platelets were not studied. Fibrinogen was low in one advanced case with bleeding from the gums and purpura. Other factors were normal in the other cases.

4. Chronic Lymphatic Leukemia: Platelets were not studied. Other factors were normal.

We shall report one case of pernicious anemia in full, since it seems to illustrate the bleeding type of this disease, and we shall mention other cases as they control these observations.

13. Addis, T.: The Pathogenesis of Hereditary Haemophilia, *Jour. Path. and Bacteriol.*, 1911, xv, 427.

14. Whipple, G. H., and Hurwitz, S. H.: Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning, *Jour. Exper. Med.*, 1911, xiii, 136.

15. Whipple, G. H. Fibrinogen: 1. An Investigation Concerning its Origin and Destruction in the Body, *Am. Jour. Physiol.*, 1914, xxxiii, 50.



## CASE REPORT

*History.*—P. L. C., aged 26, salesman, unmarried, was admitted June 3, 1914. Complaint, "Washed-out looking—weakness." Family history and habits are entirely negative. There is no history of bleeding in the family.

*Previous Medical History.*—Measles and diphtheria in childhood. No history of whooping-cough, scarlet fever, typhoid, pneumonia, pleurisy, nor malaria. Cardiorespiratory: no history of dyspnea, nor edema of the feet nor ankles. He has never been subject to colds, tonsillitis, chronic cough nor night sweats. Gastrointestinal: digestion always has been good. "Can eat anything." He has never had periods of vomiting nor epigastric distress. Genito-urinary: he has had no polyuria, dysuria nor nocturia. Nervous: there is no history of paralysis, injury nor operation; of areas of anesthesia nor paresthesia. No headache nor vertigo were present prior to the present illness. For the past three years he has noticed that the sight of his left eye has been somewhat diminished and indistinct.

*Present Illness.* In August, 1913, the patient's friends called his attention to his loss of color. From this time until March, 1914, the patient kept at his work and took iron with fair steadiness, but became constantly paler and more yellow. About May 10 severe occipital and frontal headaches developed. These lasted all day and were accompanied by periods of vertigo, especially noticeable when the patient suddenly sat upright. At the same time there was marked weakness in the muscles, with dyspnea and frequent attacks of sharp cramps in the legs when walking. Three days ago the headaches became less severe, but his appetite disappeared completely. There were no nausea, vomiting, gastric pain, nor discomfort with this. Two weeks ago he noticed dark colored stools on one occasion. There has been no history of large gastric nor intestinal hemorrhage. For several weeks there has been a marked tendency to bleed from the gums. The patient has been compelled to stop brushing his teeth as this starts bleeding which will last several hours.

Of late there has been increased dimness of vision in both eyes. His best weight was 138 pounds one year ago; present weight 124 pounds.

*Physical Examination.*—The patient subjectively is entirely comfortable. Skin is very pale, yellow, moist and smooth.

Eyes: Pupils are equal, round, regular and react promptly to light and distention. There is no nystagmus or strabismus. Fundus: O. D. disc is pale, vessels over it are poorly made out. Entire remaining area of fundus is covered with radiating hemorrhage. O. S. disc is outlined with fair sharpness. Hemorrhagic condition similar to that of O. D. is present.

Ears and Nose: Normal.

Mouth: Mucous membranes are very pale. Teeth are in good condition. At the junction of teeth and gums there are a few small blood clots. Tongue is protruded in mid-line without tremor. Tonsils are not enlarged.

Neck: Normal.

Chest: Lungs are clear, resonant and normal throughout.

Heart: There is no enlargement. There is a soft systolic murmur obscuring the first sound. This is well heard at the apex but is not transmitted to the axilla. At the base a rough, blowing systolic murmur is present, best heard in the third left interspace. Pulmonic second is greater than aortic second.

Pulses: Are regular, rapid, equal, synchronous and collapsing. Rate 128. Marked pistol shot sound is heard in the groin. Blood-pressure: systolic, 145; diastolic, 70.

Abdomen: No masses, tenderness, nor rigidity made out. Slight distention is present.

Liver is not enlarged.

Spleen is not enlarged.

TABLE 1.—FACTORS OF COAGULATION AND BLOOD EXAMINATIONS

[illegible]



Extremities: There are no edema, scars, cyanosis, or sclerosis of peripheral vessels. Color of the skin everywhere is very light yellow.

Reflexes: Knee, ankle, biceps, triceps, supinator, and pronator reflexes are easily obtained and very active. There is a marked patellar clonus. No ankle clonus, Gordon sign, Oppenheim sign, nor Babinski sign made out.

On admission the temperature was 99.2 F. Pulse, 128. Respiratory rate, 21.

#### BLOOD EXAMINATIONS AND CLINICAL NOTES

June 4. Blood:

Hemoglobin	29 per cent.
R. B. C.	752,000
W. B. C.	3,200
Platelets (23)	2,800

Differential Count: Polymorphonuclear neutrophils, 54 per cent; large mononuclear cells, 4 per cent.; lymphocytes, 41 per cent.; eosinophils, 1 per cent. Red cells show very slight anisocytosis and poikilocytosis, no polychromatophilia, stippling, or basophilia. No myelocytes, normoblasts, or megaloblasts are seen.

The puncture wound from which blood was taken for counting bled for forty-five minutes and was finally checked with nitrate of silver. This prolonged bleeding time was constant and necessitated subsequently the use of a very fine needle. Warned by this experience, the venous punctures recorded later were made with a fine needle and no trouble occurred.

Urine: Negative.

Wassermann reaction blood serum, negative.

The patient was at once placed on ascending doses of Fowler's solution, dilute hydrochloric acid with meals, and forced house diet. He was kept at rest in bed out of doors all of the time.

June 5, blood obtained by venous puncture.

Coagulation time, twenty-seven minutes. (Howell's method.)

TABLE 2.—CASE P. L. C. DETERMINATION OF ANTITHROMBIN

Thrombin, Drops	Heated Plasma, Drops	Fibrinogen, Drops	Result
4	1	10	Clot in 7 hours.
5	1	10	Clot in 34 minutes.
6	1	10	Clot in 18 minutes.
CONTROL C. K. D.			
4	1	10	Faint clot in 27 minutes; firm clot in 7 hours.
5	1	10	Clot in 37 minutes.
6	1	10	Clot in 18 minutes.

#### PROTOCOLS

The following protocols illustrate the methods used for determining antithrombin and prothrombin. For further studies of these factors and for their correlation with the changing blood picture, reference must be made to Table 1.

Antithrombin was determined by Howell's method. The test plasma is heated slowly to 60 C. and then centrifugalized to throw down the fibrinogen which has been precipitated. If a drop of the supernatant fluid is added to a known thrombin solution it can be shown to delay the action of this thrombin on fibrinogen most markedly. In every test the supposedly abnormal plasma

must be compared with plasma from a normal individual, the two being treated in the same way, their comparison indicating the abnormality, if it exists.

The patient's antithrombin was entirely comparable to that of the control and in this factor no abnormality existed. For tests made on June 17 and following dates heated plasmas were diluted 1:1 with 0.9 per cent. NaCl in order to shorten the time necessary for the experiment.

Prothrombin was determined by recalcifying oxalated plasma. Ability to invert a 10 mm. tube without dislodging the clot has been taken as the end-point throughout our entire series of observations on prothrombin. In these tests, as with antithrombin, comparison with normal plasma is necessary. Prior to July 7 the test bloods and the controls were centrifugalized simultaneously to obtain the plasma, but the duration of centrifugalization varied on different occasions. On and after this date the same speed and same time were used.

TABLE 3.—CASE P. L. C. DETERMINATION OF PROTHROMBIN

Oxalated Plasma, Drops	0.5 Per Cent. CaCl <sub>2</sub> , Drops	Result
5	2	Invertible in 19 minutes.
5	3	Invertible in 25 minutes.
5	4	Invertible in 25 minutes.
5	5	Invertible in 72 minutes.
CONTROL C. K. D.		
5	2	Invertible in 11 minutes.
5	3	Invertible in 10 minutes.
5	4	Invertible in 10 minutes.
5	5	Invertible in 12 minutes.

The patient's plasma coagulated more slowly than the control, indicating a prothrombin deficiency.

Fibrinogen was determined by the heat coagulation method: 10 c.c. of oxalated plasma are heated to 60 C. and kept at this temperature for twenty minutes. The resultant coagulum is filtered off, washed and weighed. This process is adequate for showing gross alterations in fibrinogen but very inaccurate for small variations.

*Fibrinogen.*—0.4204 gm. in 100 c.c. oxalated plasma.

June 10: For the past two days the patient has been spitting blood constantly and this evening vomited 500 c.c. of dark bloody material. He refuses nourishment and appears to be failing fast.

June 11: Condition is unimproved. Transfusion was decided on and 750 c.c. of whole blood were introduced by the indirect method from the patient's father. During exposure of the patient's veins there was a large amount of troublesome oozing. This occurred in subsequent transfusions, but always decreased as the new blood was given. About one-half hour after transfusion a few purpuric spots appeared on the patient's forearms. Bleeding from the gums stopped promptly and there was no subsequent hemoglobinuria nor elevation in temperature.

June 12: Transfusion has resulted in an increased platelet count and increased prothrombin. Fibrinogen has risen slightly but not enough to be significant.

June 14: Bleeding from the gums has recommenced.

June 16: Oozing from gums continues. Pulse rate has risen. The rapidly falling red count is an indication for a second transfusion.

TABLE 4.—ANEMIC CASES WITH SLIGHTLY DECREASED PROTHROMBIN

Case	Prothrombin		Hemo- globin, Per Cent.	R. B. C.	W. B. C.	Poly- nuclears, Per Cent.	Large Round, Per Cent.	Lympho- cytes, Per Cent.	Eosino- phils, Per Cent.	Nucleat- ed Cells
	Case, Min.	Control Min.								
VI	2-9	30	67	2,400,000	5,400	54	6	38	3	0
	3-9½	8								
	4-10	8								
	5-13	8½								
III	2-11½	9	43	1,080,000	4,600	70.5	5	23	1	0
	3-12	9								
	4-12	9								
	5-11½	9								
IV	2-9	6	60	1,724,000	6,400	83	3	10	4	6
	3-9	5								
	4-9	5								
	5-12	5								
V	2-0	6	21	620,000	3,000	68	3	29	0	0
	3-9½	5								
	4-9½	5								
	5-11½	5								

June 17: 750 c.c. of blood were given. There was immediate cessation of bleeding and immediate improvement.

June 20: Gums are not bleeding and the patient is in fine spirits, with excellent appetite. Prothrombin observed on this day parallels the control.

June 24: Gums bled severely all last night and are bleeding this morning. Pulse is weak. 750 c.c. of blood by indirect transfusion from father caused immediate cessation of bleeding and general improvement.

June 30: A great deal of bleeding from the gums recurred yesterday and last evening. During the night 50 c.c. of defibrinated human blood were injected intramuscularly. To-day the bleeding is not so rapid nor profuse and clots tend to form on the bleeding surfaces. Transfusion was again done, 650 c.c. being given. Hemorrhage stopped at once and a comfortable night's sleep ensued.

July 4: Patient has developed a sore throat with peritonsillar swelling on the right side. Gums bled constantly all afternoon and he vomited his supper with a quantity of swallowed blood.

White blood cells, 2,400. No increase of leukocytes was noted with this infection, which however, was severe enough to send the temperature to 102 F.

July 5: Gums are bleeding more severely; 11 c.c. human blood serum were given intramuscularly.

July 6: Fowler's solution was omitted; 10 c.c. human blood serum were given intramuscularly. This injection was followed by slight abatement of



bleeding during seven or eight hours, but then it started again and became very severe; 0.2 gm. salvarsan was given intramuscularly.

July 7: Excessive bleeding from the gums was present this morning and after a very restless night. Defibrinated human blood, 44 c.c., were given in the morning but the bleeding was not affected in the least: 750 c.c. of blood were given by transfusion during the afternoon and bleeding ceased immediately.

July 14: Slight oozing is present this morning between the two upper right pre-molars.

July 16: Salvarsan, 0.2 gm., was given intravenously.

After this date the patient's course continued much the same. On July 21 he received 750 c.c. of blood and on July 29, 900 c.c. and 0.2 gm. of salvarsan intravenously. These transfusions like the others were necessitated by a rapidly falling blood count due to bleeding from the gums and to failure of regeneration. Thorough removal of tartar collections from the teeth remedied somewhat the bleeding tendency but did not prove of permanent value. August 10 splenectomy was proposed and refused. Following refusal of operation the patient left the hospital for his home. He was seen one week later and was evidently failing fast. In ten more days he died and no autopsy could be obtained.

#### DISCUSSION OF CASE AND CONCLUSIONS

If we consider the entire course of this anemia it seems to have been distinguished chiefly by failure to regenerate blood-cells and by a tendency to bleed. In a recent analysis of aplastic pernicious anemia, Musser<sup>16</sup> emphasizes certain essential characteristics of this disease. These are:

1. Young males are most frequently affected.
  2. Remissions do not occur.
  3. Subcutaneous hemorrhages and hemorrhage from mucous membranes are extremely frequent. In four of the fifty-nine reported cases sudden hemorrhage was the first manifestation of the disorder.
  4. Fever is a constant symptom and often reaches a high point in the disease. In our case fever was constant, but 102 F. was the highest point reached.
  5. A low color index is the rule. This was not observed by us, the color index being constantly above 1.
  6. Leukopenia is constantly present and is caused by absence of granular forms. Leukocyte counts rarely exceed 2,000 and polymorphonuclear forms constitute from 8 to 20 per cent., instead of the usual 70 per cent. There is relative lymphocytic increase.
- We noted constant decrease of polymorphonuclear cells with increased lymphocytes, but our percentages have never been so marked as those mentioned by Musser.

16. Musser, J. H.: Study of a Case of Aplastic Anemia, *THE ARCHIVES INT. MED.*, 1914, xiv, 275.

7. Nucleated red forms, polychromatophilia, stippling and poikilocytosis are absent. Anisocytosis is found occasionally, with a tendency to macrocytosis. In twenty-five differential counts we found nucleated red cells ten times, three being the highest number seen. Other characteristics of the red cells corresponded very well with the ruling observations in these anemias.

It seems safe to regard the case as one of fairly complete aplasia. We have not found any extensive studies of the factors of coagulation in bleeding anemias. Musser records a prolonged coagulation and bleeding time in his case, and also notes the fact that 20 c.c. of horse serum with 1 gm. doses of calcium lactate four times a day did not check the tendency. Whipple<sup>2</sup> reports a case of undoubted aplastic anemia in which there was epistaxis and constant uncontrollable oozing from the gums. This patient was given 500 c.c. of defibrinated blood by indirect transfusion, with no effect on the hemorrhagic process. Bleeding time was prolonged, but coagulation time appeared normal. Blood was taken from the heart one hour and twenty-five minutes after death and an increase in antithrombin found. Prothrombin was normal and fibrinogen undetermined. The prothrombin and antithrombin studies used in this case were not subjected to the controls which Howell's later paper emphasized as necessary.

In our case we have noted the following facts:

1. Coagulation time was distinctly prolonged once only (July 17); bleeding time was always long.
2. Platelets were always far below normal and were not consistently increased by transfusion.
3. Antithrombin was consistently normal and was not altered by transfusion.
4. Fibrinogen was normal throughout and was unaffected by transfusion.
5. Prothrombin was constantly decreased, but was subject to transient slight increase by transfusion.

We have felt that throughout the entire clinical course of this patient the prothrombin reaction has given us an excellent indication of the effective clotting power of the plasma. The end-point used in the test expresses complete solid coagulation. Clotting may begin in normal time, but the process, instead of requiring a few minutes as in ordinary plasmas, takes many minutes. We have been interested to note that the plasma from other cases of pernicious anemia, essentially formative in character, shows the same tendency, but to a very slight degree. In none of these, however, has there been a history of hemorrhage and all have been regenerative and have passed into periods

of remission. Table 4 presents four such cases. Unfortunately, these observations are not accompanied by platelet counts, the importance of this factor being unappreciated when they were made. Fibrinogen and antithrombin were normal and the blood picture indicates the severity of the anemia.

Our studies seem to emphasize the following points:

1. Prothrombin is diminished slightly in all cases of pernicious anemia.

2. This diminution is not great and is unimportant if active regeneration is in progress.

3. Antithrombin and fibrinogen are normal even in the presence of very low cell counts.

4. In one case in which there has been pronounced diminution in prothrombin, platelet counts have been strikingly low, and the picture throughout has been that of fairly complete aplasia.

We wish to express our thanks to Dr. K. R. Drinker for many fibrinogen determinations throughout this work.

## THE ORIGIN OF THE PROTEINS OF NEPHRITIC URINE \*

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From time to time attempts have been made to determine the source of the protein present in albuminous urine. Chemical methods are, in most forms of albuminuria, entirely incapable of distinguishing between blood proteins, kidney proteins and urinary proteins. The most definite exception to this statement is furnished by the peculiar protein of "myelopathic albumosuria," which is distinctly different from any protein found in normal blood or tissues. With the advent of the precipitin reaction came the possibility of distinguishing sharply between proteins from different species of animals, which made it feasible to investigate the urinary proteins in relation to their original source, i. e., to determine whether they come unchanged from the food proteins, or have the character of human proteins. Several studies of this kind have been reported, but not with constant results. So discordant and widely scattered is the literature on this topic that it has seemed advisable to collect and analyze the evidence at some length.

All are agreed that foreign proteins introduced parenterally are at least in part quickly excreted by the kidneys in unchanged form, which establishes the fact that the kidney *can* excrete proteins coming to it from the blood, whatever bearing this fact may have on the question as to whether urinary proteins in nephritis come directly from the blood or not.

Ascoli<sup>1</sup> found by means of the precipitin test that, after eating eggs, the urine of healthy men and of nephritics gives reactions for both egg and serum proteins. In some individuals, however, he was able to demonstrate the presence of egg albumin in the blood and not in the urine, showing that there may be a certain amount of foreign protein absorbed unchanged and yet not eliminated in the urine in demonstrable quantities. He found that after eating beef or chicken the corresponding proteins may be demonstrable in the urine, in case they cause albuminuria.<sup>2</sup> Inouye<sup>3</sup> also found that precipitin reactions are given with anti-egg serums by the urine of some patients after eating excessive amounts of raw egg, but not by all. It would seem that infants are more likely to absorb proteins unchanged than adults, and Lust<sup>4</sup> found that, especially in diseased conditions of the alimentary canal in infants, egg-white may be detected in the urine by both precipitin and anaphylaxis

\* Submitted for publication Dec. 4, 1914.

<sup>1</sup> From the Department of Pathology, University of Chicago.

1. Ascoli: München. med. Wehnschr., 1902, xxvi, 734.

2. Ascoli: München. med. Wehnschr., 1903, I, 201 and 1761; Ztschr. f. physiol. Chem., 1903, xxix, 283.

3. Inouye: Deutsch. Arch. f. klin. Med., 1903, lxxv, 378.

4. Lust: Jahrb. f. Kinderh., 1913, lxxvii.

reactions. Bovine protein is much less readily demonstrated in the urine after feeding.

On the other hand, using the extremely delicate anaphylaxis test, which can detect much smaller quantities of the protein than the precipitin test, one of us was unable to demonstrate the presence of egg proteins in the urine of healthy men after eating large quantities of raw egg-white, whether albuminuria was produced or not.<sup>5</sup> If there was albuminuria the reactions were only for human proteins and not for egg proteins. But Minet and Leclercq<sup>6</sup> found that the urine of both normal and nephritic patients who have been given egg-white and milk may sensitize guinea-pigs to these same proteins; ordinary nephritic urine, they state, sensitizes only to human serum. Unfortunately their work is published only as a brief note, which does not permit of critical consideration.

Hecker<sup>7</sup> examined the urine of six infants, fourteen children, and three adults and obtained precipitin reactions with antibovine serum with the urine of one infant and five children. In five of these six cases the urine also reacted with antihuman serum, and in one for a time only the bovine reaction was obtained. This result, however, is not duplicated by Krasnogorski,<sup>8</sup> who examined by both the precipitin and the complement fixation reactions the urine from twenty children, and in no case could he demonstrate the presence of the proteins which were being received in the food.

Whether the urinary protein in nephritis comes from the blood through damage to the capillary walls, as is commonly assumed, or is derived from the renal epithelium, is not a new question, but renewed interest is given to it by the suggestive studies and theories of nephritis and edema of Martin H. Fischer. According to him the urinary protein is derived from the renal cells which have been dissolved under the influence of acids. We do not understand Fischer to contend that this is the sole source of the urinary protein, but it is evident from the general considerations in his book that he looks on this as the most important source. Since our biologic methods have been refined so that, at least under certain conditions, different proteins from the same animal may be distinguished, it would seem feasible to investigate by these methods the source of the urinary proteins in albuminuria, and to determine whether the urinary protein is a blood protein, or is derived from the renal tissue, or is a mixture of the two, or, possibly, is entirely distinct from either.

The principle involved is that of saturation or exhaustion of common antibodies in immune serum, so that the specific antibodies which are left can then be detected. Thus, if an animal is immunized to a mixture containing protein *A* and protein *B*, its serum will react with either protein. After saturating all the antibodies for *A*, by permitting reactions to occur with enough of *A* to combine them all, the anti-serum should still contain antibodies for *B*, which can then be demon-

5. Wells, H. G.: Jour. Am. Med. Assn., 1909, lxiii, 863.

6. Minet and Leclercq: Compt. rend. Soc. de biol., 1912, lxxiii, 464.

7. Hecker: München. med. Wchnschr., 1909, lvi, 1875.

8. Krasnogorski: Ztschr. f. Kinderh., 1912, iv, 526.

strated. For example, it is practically impossible to prepare an extract of kidney or other organ which will not contain more or less blood proteins, no matter how carefully we may wash out the organ before extracting the proteins, hence, if we immunize a rabbit with such an extract, its serum will presumably contain antibodies for kidney proteins and also for blood proteins.<sup>9</sup> To demonstrate that the human kidney does contain antigenic proteins distinct from those of the blood of the same animal we may take such an antikidney serum, permit it to react with human blood-serum until it will no longer give a precipitate with fresh quantities of blood-serum, and then test it with kidney extract; the production now of a precipitate with the kidney extract is presumptive evidence that this extract contains some antigen which is not present in the blood-serum of the same animal.

By using this saturation method, Grund<sup>10</sup> demonstrated readily that human liver, kidney and spleen contain specific organ antigens. That is, antisera for these several organs, when saturated with the homologous serum, would still give a precipitin reaction with the specific organ extract; or, conversely, antiserum for human blood when saturated with the organ extracts was still reactive with blood-serum. It was much more difficult to secure evidence of specificity between the different organs, especially between liver and kidney, although the differentiation of these organs from muscle was well defined. Numerous other more recent studies have shown much the same result, namely, that there are organ-specific proteins which can be differentiated by the precipitin reaction through the saturation method, but that this is not easy to do. Apparently in general the serum is more easily differentiated from the organ proteins than are the latter from each other.

This same principle of saturation can be utilized with the anaphylaxis reaction, as has been shown in a series of experiments with the proteins of the hen's egg and with certain vegetable proteins by Wells, and Wells and Osborne,<sup>11</sup> a fact which strongly supports the hypothesis that the refractory or desensitized state of guinea-pigs recovered from anaphylactic reactions depends on an exhaustion of the specific antibodies that are responsible for the anaphylactic state. Here the procedure is to inject the sensitized guinea-pig with one of the antigenic proteins until it no longer reacts, and then, after an interval of twenty-four to forty-eight hours, inject the other antigenic protein. A reaction with this second protein indicates that it or a corresponding antigen

9. See, for example, Minet and Bruyant, *Compt. rend. Soc. de biol.*, 1911, lxxi, 166.

10. Grund: *Deutsch. Arch. f. klin. Med.*, 1906, lxxxvii, 148.

11. Wells and Osborne: *Jour. Infect. Dis.*, 1911, ix, 147; 1913, xii, 341.



was present in the material used for sensitizing, as well as the antigen which sensitized to the first protein to which the animal has been made refractory.

We can find in the literature little evidence bearing on the possibility of a renal origin for the protein of nephritic urine, as tested by the biologic methods. Grund,<sup>10</sup> in the paper previously referred to, reports the following experiments: Antirenal serum was saturated with blood serum and thus made specific for renal proteins, and was then found to give *no* precipitin reaction with urine protein from ten different cases, even when it had given a good reaction with the same urine before being saturated with serum. Anti-serum for human serum proteins, which had been saturated with renal extract, did give reactions with the urine from four cases of nephritis. These results indicate that urinary proteins, at least in nephritis, come from the blood and do not exhibit the biologic characteristics of specific renal proteins. As Grund states, however, the possibility that small quantities of renal protein may be present in the urine is not excluded by these experiments, but, if present at all, it presumably is in very small amounts.

Later, a more extensive paper was published as an inaugural dissertation by Eva Moritz.<sup>12</sup> She found that urinary protein gives a precipitin reaction with antiserum from a rabbit immunized with urinary protein, even after saturation of the antiserum with human serum; likewise urinary protein saturated with antiserum for human blood is still reactive for antiserum for urine proteins. These experiments indicate that urinary protein is different from blood protein, which is quite the opposite from the finding of Grund. With antikidney serums the results were more ambiguous, but they generally gave reactions indicating that blood proteins and urinary proteins are not identical, but they did not show conclusively a difference between renal proteins and urinary proteins. Thus, two antirenal serums which reacted with both renal extract and urine protein, did not react with blood serum; also, antiurine serum when saturated with human serum still reacted with both urinary and renal proteins. Other antirenal serums were obtained, however, reacting with human serum and kidney extract, but not with urinary protein. Hence the conclusion is drawn by this investigator that urinary protein is not identical with either blood protein or the specific renal protein, and that if renal constituents are present in nephritic urine they must be extremely small in quantity. Urinary protein is, according to these deductions, a specific protein of itself, different from either blood or kidney cell proteins.

More recently Doerr and Pick<sup>13</sup> have reported experiments on the antigenic properties of urine proteins, and in their discussion they refer to certain other workers in the field, but unfortunately without quoting references whereby the original articles could be consulted. Among their citations is an article by Landsteiner and v. Eisler, who obtained precipitins by immunizing with normal human urine, which reacted with urine and with extract of human kidney; but they found that antisera produced by immunizing with human blood caused little or no reaction with normal human urine, and hence concluded that the antigen of normal urine must be different from the antigen of serum and perhaps derived from the kidney itself. The antisera obtained by these authors by immunizing with urine were not very strong, and some subsequent observers have doubted that the reactions observed were true precipitin reactions. Doerr and Pick, however, also found that the serum of a rabbit immunized with normal human urine (giving no chemical reactions for protein) gave precipitin reactions with extracts of human kidney, but not

12. Moritz, Eva: Beiträge zur serologischen Untersuchung der Harneisweisses, Freiburg i. Br., Speyer and Kaerner, 1911.

13. Doerr and Pick: Ztschr. f. Immunitätsf., 1914, xxi, 463.

with extracts from other organs or human serum. The antigen of normal urine also shows a characteristic seen with renal extracts, in that antiserum for horse urine contains amboceptors that are lytic for sheep erythrocytes and toxic for normal guinea-pigs. Furthermore, the amount of protein present in nephritic urine has no relation to the amount of this peculiar heterogenetic antigen found in normal urines, which is characterized by not being specific for the species from which it originates. Hence Doerr and Pick seem to have demonstrated that in normal urine there is an antigen which probably is derived from the renal cells and not from the blood, but which probably is not the same as the protein excreted in nephritis. Their experiments do not establish the source of the latter.<sup>14</sup>

While we were engaged in the present investigation, G. Salus<sup>15</sup> published a study of the antigenic properties of "organ plasma" prepared by Pohl's method, and found that such organ plasma, if free from blood, is entirely distinct from the antigens of blood. That is, in his experiments, antibodies (precipitins, anaphylactins, and complement-binding) for serum did not give reactions with organ plasma, or conversely. He then took up specifically the question of the origin of the protein in nephritic urine on the basis of this observation, and summarizes his results as follows: Antiserum for human serum gives precipitin reactions with nephritic urine but not with kidney protein, and antiserum for nephritic urine reacts with human serum; hence the urine must contain the same antigens as the serum. Antiserum for human kidney contained neither precipitins nor complement-binding antibodies for either human serum or nephritic urine; hence the latter does not contain the antigens characteristic of kidney tissue. Guinea-pigs sensitized with nephritic urine or blood serum did not give anaphylaxis reactions with kidney plasma, and animals sensitized with this plasma were reactive to serum or urine only when the plasma gave distinct reactions for blood. He therefore concludes that the protein of nephritic urine must be serum protein, and not renal tissue protein.

Examining the protocols, however, we find that these conclusions are based on a small number of experiments. For example, the statement that human serum does not sensitize to human kidney plasma is based on *one* experiment; while the reverse reaction was tried but twice. As for the experiments between kidney plasma and urine, we find but six; of three guinea-pigs sensitized with human kidney, two gave no reactions with human nephritic urine, and one gave a slight reaction; of three sensitized to nephritic urine, one gave no reaction to human kidney, one gave a slight reaction and one died; the positive reactions are ascribed by Salus to admixed blood or pus. Surely no one familiar with the requirements of anaphylactic experiments would be willing to draw positive conclusions from such a meager and variable set of results as this, and the statement that has been made that these experiments settle Fischer's theory of nephritis is totally unwarranted.<sup>16</sup>

From this review of the literature it is apparent that the available evidence on the origin of the urinary protein, whether in alimentary albuminuria or in nephritis, is entirely contradictory, and therefore of little value in drawing any conclusions. Presumably, part of the contradictions depend on the difficulties inherent in the available methods

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14. In another paper (Biochem. Ztschr., 1914, lx, 257) discussing the antigenic property of extract of horse kidney, they note that it is not anaphylactogenic for guinea-pigs, but do not state whether the antigen of horse urine exhibits the same characteristic.

15. Salus, G.: Biochem. Ztschr., 1914, lx, 1.

16. A controverted theory of nephritis, editorial, Jour. Am. Med. Assn., lxii, 1971.

for distinguishing, even by the biologic reactions, between different proteins coming from the same animal. There should be, it would seem, no difficulty in differentiating egg or milk proteins from human proteins, nevertheless there are remarkable contradictions in the reports concerning the presence of foreign proteins in the urine in alimentary albuminuria. This being so, the distinction of the closely related proteins of urine, kidney and serum of the same species, must be a task of exceeding difficulty. It is evident, therefore, that there is need for more work, and especially for more careful work, in this field, and we have endeavored to seek further evidence on the disputed points.

#### AUTHORS' EXPERIMENTS

Our experiments were conducted as follows:

Urinary protein was obtained by collecting large amounts of urine from patients with chronic parenchymatous nephritis, preserving with chloroform, dialyzing against cold running water until but a small proportion of the crystalloids remained, and then rapidly drying at room temperature by exposing in thin layers to an air current. The product thus obtained was found on analysis to contain 39.4 per cent. of soluble coagulable protein in one preparation, and in another 58.5 per cent.

Kidney protein was obtained from fresh, practically normal human kidneys, by washing the chopped tissue to remove as much blood as possible, extracting with water in the cold, and preserving the watery extract with chloroform. This extract contained 2.5 per cent of soluble, heat-coagulable protein. It contained, of course, a considerable proportion of blood, but by use of the saturation method this difficulty should be overcome in biologic tests.

Guinea-pigs of about 250 to 300 grams were sensitized with the following amounts of each material:

Urinary protein, .005 gm.

Kidney protein, 0.5 c.c. extract, or 0.0125 gm. protein.

Human serum, 0.1 c.c.

After an interval of twenty to thirty days they were injected with the heterologous protein in the following amounts:

Urinary protein, 0.05 to 0.10 gm. crude material, or 0.020 to 0.058 gm. protein. Kidney protein, 2 to 5 c.c. of extract, or 0.05 to 0.125 gm. protein.

Human serum, 0.1 c.c. to 0.6 c.c., after heating one hour at 56 C. to remove "primary toxicity."

A second dose of the same amount of heterologous protein was given twenty-four to seventy-two hours later, to insure saturation of all antibodies specific for the foreign proteins which the animal might have developed. This was followed forty-eight to seventy-two hours later by an injection, usually of the protein used for sensitizing, to ascertain if there had been developed antibodies specific for this protein and not reacting with the heterologous protein. Frequently the third of our proteins was injected later, to see if any antibodies for this protein were present.

Control experiments showed that our preparations were capable of producing a severe, characteristic anaphylaxis reactions when the same protein was used for both sensitizing and intoxicating dose.

In view of the character of the results obtained, it scarcely seems necessary to give detailed protocols; hence the experiments are summarized in the accompanying table:

Abbreviations used in tables:

- U—Urine protein.  
 S—Human serum.  
 K—Kidney protein.  
 A—Human ascites fluid.  
 0—No anaphylactic reaction.  
 +—Slight anaphylactic reaction.  
 ++—Moderate anaphylactic reaction.  
 +++—Severe anaphylactic reaction.  
 ±—Doubtful anaphylactic reaction.  
 d—Fatal anaphylactic reaction.

TABLE SHOWING REACTIONS IN ANIMALS SENSITIZED TO VARIOUS PROTEINS

SENSITIZED TO KIDNEY PROTEINS *			
1. K d	—	—	—
2. K d	—	—	—
3. U ++	U +	U 0	S +
4. U ++	U +	K +	S +
5. U ++	U +	K +	S +
6. U ++	U 0	K 0	S +
7. S ++	S +	K +	U +
8. S ++	S +	K +	U +
9. S ++	S +	K 0	U +
10. S ++	S +	K 0	U +

\* In all these experiments, unless otherwise specified, the interval after sensitization before injecting the first intoxicating dose was twenty to thirty days, and between each succeeding dose it was two days.

SENSITIZED TO SERUM PROTEINS			
1. S d	—	—	—
2. S d	—	—	—
3. K ++	K +	S +	U 0
4. K ++	K +	S +	U 0
5. K ++	K 0	U 0	—
6. U d	—	—	—
7. U d	—	—	—
8. U d	—	—	—
9. U ++	U ±	S 0	K 0
10. U ++	U ±	S 0	K 0

SENSITIZED TO URINE PROTEINS			
1. U +++	—	—	—
2. U +++	—	—	—
3. S ++	S 0	U 0	K + †
4. S ++	S 0	U 0	K +
5. S ++	S 0	U 0	K +
6. S ++	S 0	U 0	—
7. K ++	K 0	S 0	K +
8. K ++	K 0	S ±	K +
9. K ++	K 0	U 0	K 0
10. K ++	K 0	U 0	K +
11. K ++	K +	U 0	—
12. K ++	K +	U 0	—
13. K ++	K +	U 0	—
14. S ++	S +	U 0	K 0
15. S ++	S +	U 0	K 0

† The injections recorded in this column were made seven days after the last preceding injection in Animals 3, 4, 5, 7, 8, 9 and 10, so that there had been time for a new sensitization to have resulted from the first intoxicating dose given eleven days before.

SENSITIZED TO ASCITES FLUID		
	U 0	A 0
1. U +	—	—
2. U d	U 0	A 0
3. U +	U 0	A 0
4. U +	U 0	A 0
5. U + +	U 0	A 0
6. K + +	K 0	A 0
7. K + + +	K 0	—
8. K + + +	K 0	A 0
9. K + +	K 0	A 0

Examining this table we find that the results are as uniform as can be expected in such a series of anaphylaxis experiments, permitting conclusions to be drawn with reasonable confidence. Without exception, guinea-pigs sensitized to any one of the three preparations—urinary proteins, renal extract and serum or ascites fluid, react strongly to either of the other two. This must mean that identical antigens are present in each. We also find that after saturation with the heterologous antigen the animals are refractory to the antigen used for sensitizing, which may be interpreted as indicating the absence in any one of the three proteins of any antigen not present in the other two which can be demonstrated by the method employed. That there may not be such specific antigens present in urine, serum and kidneys, as maintained by some previous observers, we do not pretend to deny on the basis of these experiments. Other methods may demonstrate them, but our experience with the saturation method in the detection of mixed antigens by anaphylaxis has indicated that this method usually is efficient.<sup>17</sup>

#### CONCLUSIONS

The literature on the source of the proteins in the urine of nephritics contains such conflicting statements that it is impossible to decide whether urinary protein is derived from the blood or the kidneys, or is a specific protein distinct from the proteins of either blood or kidney. A series of experiments by the anaphylaxis method gave no evidence of the existence of antigens in either urine or kidney distinct from each other or from the antigens of human serum. This result does not answer the question of the origin of urinary protein, but merely indicates the inadequacy of the anaphylaxis method for the solution of the problem.

17. We also made attempts to develop precipitins and complement fixation antibodies by immunizing rabbits with these proteins, but without success.

## MERCURY NEPHRITIS \*

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The instances of renal disease in which exclusively one portion of the anatomical structure of the kidney has received injury are so excessively infrequent that they at once excite interest as means of testing our conceptions of physiological functions of this organ and the mode of origin of some signs of disease. These conditions are, patently, those of successful experimentation. That the occasional cases of toxic nephritis in man have not been more fruitful in yielding information applicable to broader studies is due chiefly to the great rapidity and severity of the symptoms, culminating after a few days in death. Instances of fatal poisoning with mercuric chlorid are common, and there is a well recognized type of lesion found in the kidney in these cases; but as the period of life after ingestion of the poison is relatively brief, the signs and symptoms of renal injury are obscured and massed in those occasioned by a corrosive poison.

In the case of mercuric poisoning reported here the patient lived forty-one days, so that many of the features ordinarily seen in these cases, while present during the first week or more, were not sources of confusion at later periods in the disease.<sup>1</sup>

### CASE REPORT

*History.*—Mrs. A. R., aged 26, was brought to New York Hospital, May 26, 1914. She stated that she had that morning (8:30) taken six tablets for a headache. Shortly after, discovering that the tablets were mercuric chlorid, she sent for a physician. About half an hour after taking the tablets the patient vomited a large amount of material. On admission to the hospital at 10:15 a. m. the patient did not appear acutely ill. There were no excoriated areas in the mouth, though the pharynx was considerably congested. Other than some sensitiveness in the epigastrium the admission examination was negative. Lavage water containing gastric contents gave positive tests for mercury. A catheterized specimen of urine contained considerable albumin, numerous granular casts, but no blood. This specimen was not tested for mercury, but the metal was detected a number of times in the urine subsequently.

*Treatment and Course.*—Treatment was at once begun by frequent lavage of the stomach and bowel and an endeavor made to increase the fluids taken by the patient, supplemented by the Murphy drip. During the first day the

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\* From the Department of Medicine, Cornell University, and the First Medical Division of the New York Hospital.

1. The longest period of life recorded after swallowing poisonous amounts of mercuric chlorid is twenty-one days.



patient's mouth became sore, which interfered with the ingestion of anything. This symptom became worse and for two weeks there persisted an extreme degree of stomatitis and pyalism which was an obstacle to the efforts made to spare the kidneys. The irritated condition of the gut was evidenced for ten days by frequent discharges, containing much mucus and blood. This state of affairs not only made the retention of the rectal tube painful, but seemed to decrease the absorption of water from the intestine.

There was fever up to 101 F. and a leukocytosis of 20,000 during the first week, after which both temperature and leukocyte counts were normal; the systolic blood-pressure varied between 100 and 140 mm. of mercury during the whole course of the sickness.

Due to the conditions mentioned the amount of water taken by mouth and absorbed from the intestine was not as large as desired; on May 30, 900 c.c. were retained and on June 4, the tenth day of the sickness, there were noted convulsive tremors involving all the muscles. Later there was a mild general convulsion and the patient was in a stuporous state the remainder of the day. This was repeated June 7, the thirteenth day of the illness, with more severity, although the urine volume had risen to 2,000 c.c. A state of semi-coma persisted for two days. As the patient became more conscious it was evident that there existed a mild toxic psychosis. On the whole, the general condition was regarded as good during the following two weeks, and a favorable prognosis was considered because of the improving state of renal activity. Vomiting had been a troublesome symptom from the start, but during the latter part of June this symptom came more into prominence, until scarcely anything was retained in the stomach. Any fluid or food was rejected. The patient said, however, that she felt quite comfortable. Hypodermoclysis was carried on during this period at intervals. On July 2, 8 liters of saline solution were thus given. Glucose was given by enema but evidently not absorbed.

The patient's mental condition gradually became more cloudy and stuporous. For twenty-four hours before death the respiratory movements were of quite characteristic air-hunger type. The patient died on the forty-first day after taking the mercury.

Retinal examinations were made on several occasions but no abnormality noted.

The Urine: The amount varied considerably, depending chiefly on fluid intake. The average was about a liter a day, with something over two liters as the high extreme. There was not evident at any time an inability to excrete water by the kidney. There was no edema and in the last week the response to hypodermoclysis was prompt and adequate. The specific gravity of the urine was generally low, rising above 1.015 on two days, and on several being below 1.005. After the first week the amount of albumin was slight and was precipitated almost completely by acetic acid in the cold (nucleo-albumin). The urine contained considerable pus from a cystitis, and usually erythrocytes; but casts of any sort were seldom noted after the first week of the sickness. Mercury was found in all specimens of urine examined until June 21, when the tests were negative.

No study of the chlorid or nitrogen metabolism could be carried out since the ingest was made uncertain by vomiting and the patient was incontinent of urine. Two twenty-four-hour collections of urine secured by means of a retention catheter were analyzed; the sodium chlorid was just under 3 grams and the nitrogen about 6 grams. While these results are probably too low, as some urine was doubtless lost, they do not in themselves suggest a plus balance. This is supported in respect to the chlorid by absence of detectable edema. Considerable interest attaches itself to renal tests in cases of this nature, as the condition presents the essential features of an experimental nephritis in a human subject. A number of phenolsulphonephthalein tests were made and in none was there recovered a detectable amount of the test-substance.

Non-protein nitrogen of the blood was estimated three times; on June 10 it was 225 mg., on the 15th, 209 mg., and on the 26th, 238 mg. Of the last figure, 71 per cent. (176 mg.) was urea.

This history presents some interesting departures from the common course of events in cases of this sort where the duration of life is brief. Anuria was at no time a symptom, and when the amount of urine fell below normal this was adequately accounted for by a low ingestion of fluids. When the water intake was forced there was apparently a normal response in output. In contrast again with the usual picture are the convulsive seizures, muscular twitchings and the toxic psychosis. The stupor and coma that accompanies anuria induced by mercury poison in common with anuria from other causes, is so uniform in its manifestations that Ascoli separated the syndrome from that of uremia under the caption of "urinary poisoning." The salient characteristics in this clinical picture are the progressive lassitude and somnolence, gradually deepening into coma as death approaches. These are the manifestations notable in dogs after the ligation of the renal arteries, and they describe also the nervous symptoms usually evident in cases poisoned with mercuric chlorid.<sup>2</sup> Convulsions are seldom observed and only in the latter hours of life. Of those symptoms which are associated with uremia, there were observed in this case, besides the evidences of renal disease, epileptiform convulsions, muscular twitching and a psychosis of the usual toxic type. Whether this constitutes uremia must be left undetermined.

Further consideration must be based on an anatomical study.

The autopsy disclosed, besides an eroded condition of the lower bowel and degenerative changes in the liver, a remarkable nephritis which was studied with care from many sections. The following note is Dr. Elser's comment on the condition observed.

*Examination of Kidneys.*—Microscopic examination of the kidneys shows dilatation of the tubules of the cortex with extensive degeneration, necrosis and desquamation of the lining epithelium. Many of the convoluted tubules are more or less completely filled with necrotic material which, in places, is the seat of calcific deposits. Some of these masses show small colonies of bacteria. The interstitial structures are edematous and show, in places, small areas of round cell infiltration. Occasional masses consisting entirely of bacteria are found in the vessels and between the convoluted tubules. The fact that the surrounding structures reveal no evidences of reaction suggests that this represents in a large measure a post mortem development of bacteria. The glomeruli are remarkably free from pathologic changes. Slight dilata-

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2. It is of interest that Brauer, in his experimental study of the effects induced in the nervous system through poisoning with mercury, mentions that the symptoms he observed might be explained as uremia. The effects he remarked were increased reflexes, ataxia, and paralyses with convulsions as a terminal phenomenon. The worst cases of poisoning showed no nerve changes. *Deutsch. Ztschr. f. Nervenhe.*, 1897, xii, 1.

tion of the capsule is seen in places and here and there the epithelial lining is swollen and separated from the subjacent structures. Sudan III preparations show only traces of fat in the epithelial cells of some of the convoluted tubules.

The lesions enumerated above are those usually encountered in the kidney in cases of bichlorid (mercuric chlorid) poisoning.

The lesions noted are remarkably similar to those induced in animals by such poisons as uranium and tartaric acid, in that the damage done is borne chiefly by the tubular epithelium. In this case the evidence of injury was confined more strictly to one structural element — tubules — than in any sections showing experimentally induced renal lesions that have come to my observation. On this account the large non-protein nitrogen of the blood in this case of mercury poisoning is of an especial interest, recollecting that it is with uranium nephritis in animals that this phenomenon also becomes pronounced.

The other consideration that arrests attention is the absence of tangible evidence pointing toward chlorid and water retention. The data available does not permit of conclusion, although the chlorid excretion was as large as the estimated ingest. Edema was not manifest. Considerable water retention may occur, however, before edema can be demonstrated, except by weight, and a "dry" chlorid retention is well recognized. These reservations seem advisable in view of Heinecke's observation that disturbances of chlorid excretion are associated with those poisons which injure the renal tubules.<sup>3</sup>

It is not permissible to build deductions from this scanty material, but better, perhaps, to regard this case as a straw in the wind of evidence.

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3. Relevant to the discussion is a case of mild mercuric chlorid poisoning reported by Monakow since the above was written. Except during the first days of illness, there was no evidence of retention of water or nitrogen. There was, however, chlorid retention and later a minus chlorin balance. Edema was manifest. The poisoning was slight, as the patient recovered without special flushing treatment. *Deutsch. Arch. f. klin. Med.*, 1914, cxv, 227.

## THE OCULOCARDIAC REFLEX

AN ELECTROCARDIOGRAPHIC STUDY WITH SPECIAL REFERENCE TO THE  
DIFFERENCES BETWEEN RIGHT AND LEFT VAGAL AND OCULAR  
PRESSURES IN TABETICS AND NON-TABETICS \*

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### INTRODUCTION AND HISTORICAL REVIEW

In 1908 B. Aschner<sup>1</sup> first observed that pressure on the eyeball caused slowing of the pulse and decrease in the depth of respirations. He found that it would arouse stuporous, anesthetized and unconscious patients, and enable them to respond to questions. He also showed that in narcosis the oculocardiac reflex lasts longer than the corneal or pupillary reflexes. Grossmann and Miloslavich<sup>2</sup> in 1912 made similar observations, and Fabre and Petzetakis,<sup>3</sup> working six years later than Aschner, confirmed the observation that the oculocardiac reflex persists even under deep ether or chloroform anesthesia, and can be elicited after the corneal reflex has gone. It was demonstrated by Aschner that the afferent impulse of the reflex passes through the trigeminal nerve to its nucleus in the midbrain, and that the efferent passes by way of the pneumogastric nerve. By cutting the third, fourth, sixth, seventh or eighth cranial nerves he could not destroy the reflex, but by cutting the fifth the reflex was destroyed. He also showed that the inhibition of the heart was not due to increased intracranial pressure, for the relief of pressure by trephining the skull did not abolish the reflex.

Milian,<sup>4</sup> overlooking Aschner's discovery of five years before, stated in 1913 that the phenomenon of pulse-slowng resulting from ocular pressure should be called "*la signe de Gautrelet*" after one of his pupils who had been studying this reflex in his hospital for two years. This

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\* From the Hospital of the Rockefeller Institute for Medical Research, New York.

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1. Aschner, B.: Ueber einen bisher noch nicht beschriebenen Reflex vom Auge auf Kreislauf und Atmung, Wien. klin. Wchnschr., 1908, xliv, 1529.

2. Grossmann, J., and Miloslavich, E.: Ueber die Beeinflussung der Herz-tätigkeit durch Bulbusdruck, Wien. klin. Rundschau, 1912, xii, 177.

3. Fabre and Petzetakis: Persistance du réflex oculo-cardiaque pendant l'anesthésie générale, Compt. rend. Soc. de biol., 1914, lxxvi, 343.

4. Milian: Du ralentissement du pouls radial au cours de la compression oculaire dans la maladie de Basedow, Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, No. 14, p. 878.

would bring back Gautrelet's first observation to three years after Aschner's discovery. Milian found that one could obtain the normal oculocardiac reflex in a dog breathing normally, whether anesthetized or not. But if the thorax were opened and artificial respiration instituted, no slowing of the pulse followed ocular pressure, but instead the tone of the ventricles was increased. This is the experimental evidence for the existence of the reflex and the basis of its mechanism. Many reports dealing with it from a clinical aspect have now been published.

Loeper and Mougeot<sup>5</sup> investigated the condition of the oculocardiac reflex in certain varieties of gastric neurosis, namely, hypervagotonic and the hypersympatheticotonic. The former are recognized by the presence of some of the following symptoms: paleness of the face, tendency to myopia, bradycardia, low blood-pressure, moist skin, asthma, gastric hypersecretion, hyperchlorhydria, rapid gastric motility, spasmodic constipation, etc. The latter present the opposite set of symptoms. The former react to pilocarpin with sweating and salivation, but do not react to epinephrin. The latter do not react to pilocarpin, but react to epinephrin with tachycardia, hypertension and glycosuria. They found that the oculocardiac reflex was exaggerated in the hypervagotonic cases and diminished or absent in the hypersympatheticotonic. Similar results were obtained in an elaborate investigation by Gautrelet.<sup>6</sup> In several instances they claim to have accelerated the pulse rate by ocular pressure, and they explain this unusual result by stating that the reflex which is generally conveyed by the vagus at times passes over the sympathetic nerve. They consider that an individual whose pulse rate is accelerated or slowed more than ten beats per minute by pressure is abnormal, in the sense that he belongs to one or the other of the two groups named. This is a point to which reference will be made again later.

Lesieur, Vernet, and Petzetakis<sup>7, 8, 9</sup> have studied the condition of the oculocardiac reflex in epileptics. This reflex, as well as tendon and

5. Loeper, M., and Mougeot, A.: Le réflexe oculo-cardiaque dans le diagnostic des nevroses gastriques, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1913 No. 14, p. 865.

6. Gautrelet, J.: Le réflexe oculo-cardiaque, *Paris méd.*, Nov. 29, 1913, p. 583.

7. Lesieur, Ch.; Vernet, M., and Petzetakis: Sur un cas d'arrêt total du cœur par réflexe oculo-cardiaque chez un épileptique, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 9, p. 394.

8. Lesieur, Ch., Vernet, M., and Petzetakis: Contribution à l'étude du réflexe oculo-cardiaque. Son exagération dans l'épilepsie, les variations sous l'influence d'actions médicamenteuses ou toxiques, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 9, p. 440.

9. Lesieur, Ch., Vernet, M., and Petzetakis: Considerations sur les modifications des réflexes pendant la compression oculaire chez certains épileptiques, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 11, p. 510.

cutaneous reflexes, was found to be exaggerated. In their experience it was found that bromid treatment not only lessened the frequency of epileptic attacks, but also diminished the oculocardiac reflex by decreasing vagal irritability. In the same study they found that the right eye responded more strikingly and on slighter pressure than did the left. Usually, when atropin was injected subcutaneously, it abolished the oculocardiac reflex, but ocular pressure continued to inhibit the respiratory motions of the patient just as it did when no atropin was given. This they called the oculophrenic reflex. Later, the same authors<sup>10</sup> found that ocular pressure caused glycosuria in three of their six cases of epilepsy. Four showed albuminuria and all had polyuria. This reflex, they presumed traveled over the sympathetic nerve and not the vagus, because in Claude Bernard's experiments in which he punctured the floor of the fourth ventricle, he observed glycosuria in animals when the vagi were divided, but not when all the sympathetic fibers were cut.

Guillain and Dubois,<sup>11</sup> in a case of double athetosis, noticed that the athetoid movements of the face, tongue and extremities ceased during ocular pressure, but increased during any other medical manipulation. Obstinate yawning and hiccup were observed by Loeper and Mlle. Weil<sup>12</sup> to be influenced favorably by ocular pressure. In six cases of pseudobulbar paralysis, Guillain and Dubois<sup>13</sup> found that four had lost the oculocardiac reflex, and that the other two responded by an acceleration of the pulse rate. The condition of the oculocardiac reflex in various tremors has been studied by Lesieur, Vernet and Petzetakis.<sup>14</sup> Of sixteen cases of Parkinson's disease the reflex was absent in fifteen. Of four cases of multiple sclerosis the reflex was absent in one, accelerated in two and normal in one. The reflex was normal in two cases of alcoholic tremor and in two cases of senile tremor. Of six cases of general paresis the reflex was exaggerated in four and normal

10. Lesieur, Ch., Vernet, M., and Petzetakis: Glycosurie, albuminurie, polyurie provoquées par la compression oculaire, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 11, p. 515.

11. Guillain, G., and Dubois, J.: Action inhibitrice de la compression oculaire sur les mouvements anormaux dans un cas d'athetose double, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 16, p. 850.

12. Loeper, M., and Mlle. Weil: Action favorable de la compression oculaire sur certaines manifestations nerveuses et en particulier sur le hoquet, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 13, p. 631.

13. Guillain, G., and Dubois, J.: L'abolition et l'inversion du réflexe oculocardiaque dans les paralysies pseudo-bulbaires, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 12, p. 584.

14. Lesieur, Ch.: Vernet, M., and Petzetakis: Le réflexe oculo-cardiaque chez les sujets atteints de divers tremblements, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 12, p. 593; Réflexe oculo-cardiaque et maladie de Par-  
kinson, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 14, p. 599.



in two. They concluded that the oculocardiac reflex might aid in determining whether a nervous lesion was central or peripheral. It does not seem clear, however, how the differentiation is to be made, for a reflex may be either exaggerated or destroyed by a lesion of the afferent limb, center, or efferent limb of a reflex arc. The condition alone of a reflex will scarcely determine the site of a lesion.

In the study of the reflex in organic diseases of the central nervous system, Miloslavich<sup>15</sup> in 1910 was the first to observe that the reflex was absent in tabes dorsalis. Loeper and Mougeot,<sup>16, 17</sup> and Lesieur, Vernet and Petzetakis<sup>18</sup> have shown that in a majority of such patients the pulse rate is either not slowed at all by ocular pressure, or only slightly affected. Lesieur, Vernet and Petzetakis found the reflex to be absent when the Argyll Robertson phenomenon had not yet developed. In syphilis of the nervous system, other than tabes dorsalis, Loeper, Mougeot and Vahram<sup>19</sup> found that the reflex was also absent in thirty of their forty cases.<sup>20</sup> None had Argyll Robertson pupils. These patients were generally in the tertiary stage. The reflex, then, is lost both in tabes and in other syphilitic diseases of the nervous system. But there need be no necessary relation between its loss and the presence or absence of the Argyll Robertson pupil. Different results were obtained in this study concerning the condition of the reflex in syphilitic patients who are not tabetic. Further reference will be made to this later.

The condition of the reflex in Basedow's disease has aroused a great deal of interest. Grossmann and Miloslavich,<sup>2</sup> Milian,<sup>1</sup> Sainton,<sup>21</sup> and Lesieur, Vernet and Petzetakis<sup>14</sup> have shown that it is generally exaggerated in this condition. They attribute this to the hypervagotonicity present in these patients.

15. Miloslavich, E.: Ueber Trigeminus-vagus Reflex, Wien. med. Wchnschr., 1910, ix, 3051.

16. Loeper, M., and Mougeot, A.: L'absence du réflexe oculo-cardiac dans le tabes, Progrès méd., 1913, No. 52, p. 675.

17. Loeper, M., and Mougeot, A.: Absence fréquente du réflexe oculo-cardiaque dans le tabes, Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, No. 39, p. 942.

18. Lesieur, Ch.: Vernet, M., and Petzetakis: Note sur l'abolition fréquente du réflexe oculo-cardiaque dans le tabes, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 9, 446.

19. Loeper, M., Mougeot, A., and Vahram: Abolition fréquente du réflexe oculocardiaque chez les syphilitiques, Progrès méd., 1914, No. 14, p. 157.

20. The authors give no reason why the cases should be considered syphilis of the nervous system and not merely tertiary syphilis. They conclude, however, that the frequent absence of the oculocardiac reflex is evidence that the nervous system is early involved.

21. Sainton: Le réflexe oculo-cardiaque dans la syphilis de Basedow, Bull. méd., 1913, No. 60, p. 701.

The condition of the reflex in tachycardias and bradycardias has been studied by Mougeot<sup>22</sup> and Loeper and Mougeot.<sup>23</sup> They believe, in general, that in tachycardias and in bradycardias of nervous origin, the reflex is preserved, while in those of myocardial origin, it is lost. They suggest this difference as a method for distinguishing the two. Fabre and Petzetakis<sup>24</sup> observed that in the bradycardias occurring during the puerperium, ocular pressure caused auriculoventricular dissociation. Dufour and Legras<sup>25</sup> reported the case of a young woman who, having had a miscarriage a few months before, suddenly developed hypo-ovarian symptoms; that is to say, amenorrhea and loss of hair. Later she developed hyperthyroidism, indicated by the presence of exophthalmos and tachycardia. Epileptiform attacks, due, it is said, to cerebrospinal hypertension, supervened. During this time ocular pressure caused no slowing of the heart. Later, when the hair began to return, the reflex reappeared, so that during ocular pressure complete auriculoventricular dissociation took place. No mention was made as to which eye caused the dissociation. The authors do not clearly state whether the reflex was absent before hyperthyroidism developed, during it, or after the symptoms had quieted down. It does not seem likely that the occurrence of hyperthyroidism should make the reflex disappear. Its absence was more probably due to the hyposecretion of the ovaries; for the reflex reappeared when the ovaries functioned normally.

The influence of drugs on the condition of the reflex has been studied by Petzetakis<sup>26</sup> and Mougeot.<sup>27</sup> They found that atropin

22. Mougeot, A.: Tachycardie paradoxale des hypertendus et réflexe oculo-cardiaque, *Progrès méd.*, 1913, No. 51, p. 663; Le réflexe oculo-cardiaque dans les tachycardies permanentes sans arythmie, *Compt. rend. Soc. de Biol.*, 1914, No. 5, p. 205.

23. Loeper, M., and Mougeot, A.: Le réflexe oculo-cardiaque dans le diagnostic de la nature des bradycardies, *Compt. rend. Soc. de biol.*, 1914, No. 3, p. 104.

24. Fabre and Petzetakis: De la bradycardie et automatisme ventriculaire provoqué dans les suites de couches par la compression oculaire, *Réunion Obstétrical et Gynecologique de Lyon*, January 19, 1914, p. 37.

25. Dufour and Legras: Réflexe oculo-cardiaque provoquant l'arrêt du cœur. l'automatisme ventriculaire et la dissociation auriculo-ventriculaire, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, No. 14, p. 686.

26. Petzetakis: L'épreuve de l'atropine, du nitrite d'amyl et de la compression oculaire dans les bradycardies totales, *Compt. ren. Soc. de biol.*, 1913, lxxv, p. 677; De l'automatisme ventriculaire provoqué par la compression oculaire et l'atropine dans les bradycardies totales, *Compt. rend. Soc. de Biol.*, 1914, No. 1, p. 15; L'épreuve de la compression oculaire du nitrite d'amyl et de l'atropine dans le diagnostic des bradycardies totales d'origine nerveuse, *Presse méd.*, 1914, No. 17, p. 161; Abolition du réflexe oculo-cardiaque par l'atropine; son exagération par la pilocarpine; sa persistance pendant l'épreuve du nitrite d'amyl, *Compt. rend. Soc. de biol.*, 1914, No. 6, p. 247; Le réflexe oculo-cardiaque chez

0.02 mg.<sup>28</sup> injected subcutaneously abolished the reflex for a period of one to three hours. In a small portion of cases atropin exaggerated the reflex or excited automatic ventricular beats. These are the cases in which atropin retards rather than accelerates the heart rate. Pilocarpin, 0.01 gm. generally exaggerated the reflex. When amyl nitrite was given ocular pressure slowed the accelerated heart, but inhibition began after a longer latent period than occurs normally.

Various studies of the effect of the ocular pressure on the mechanism of the heart itself have been made. Mougeot<sup>29</sup> found that the reflex was generally not abolished during alternation of the ventricle. In some cases of uremia and other intoxications in which ventricular alternation was present, the reflex was lost. Its reappearance was taken to indicate amelioration in the underlying condition. It has been suggested that the loss of the reflex depends on an intoxication of the vagus nuclei in the medulla, by means of which the path of the reflex is cut. In ten of seventy-five cases, Petzetakis<sup>30, 31</sup> obtained transient dissociation of the auricles and ventricles by ocular pressure. The same arrhythmia was also observed by Gallavardin, Dufour and Petzetakis.<sup>31</sup> No mention was made of any difference between the effects produced by pressure on the right and left eyes. A little later Petzetakis<sup>32</sup> was able to conclude from a study of two cases that pressure on the left eye is more apt to cause disturbance in auriculo-ventricular conduction, while pressure on the right eye has a greater influence on rate. His explanation for the difference in effect between the two is that the right vagus is more sensitive than the left. He found two patients in whom ocular pressure caused partial heart-block and later complete auriculoventricular dissociation. The arrhythmia was prevented from appearing in these cases by the injection of atropin. Petzetakis<sup>33</sup> reported one case in which atropin had the reverse effect.

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les sujets normaux non bradycardiques, Bull. et mém. Soc. d. hôp. de Paris, 1914, No. 12, p. 562.

27. Mougeot, A.: Suppression constante par l'atropine de réflexe oculo-cardiaque, Compt. rend. Soc. de biol., 1914, No. 4, p. 162.

28. This seems to be a small dose.

29. Mougeot, A.: Le réflexe oculo-cardiaque dans l'alternance ventriculaire, Compt. rend. Soc. de biol., 1914, No. 12, p. 541.

30. Petzetakis: Réflexe oculo-cardiaque et dissociation auriculo-ventriculaire, Compt. rend. Soc. de biol., 1914, No. 10, p. 409; Automatismes ventriculaires intermittents provoqués à l'état normal, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 14, p. 727.

31. Gallavardin, Dufour and Petzetakis: Automatismes ventriculaires intermittents, spontanés ou provoqués par la compression oculaire et l'injection d'atropine dans les bradycardies totales, Arch. de mal. du cœur, 1914, vii, 1.

32. Petzetakis: Block auriculo-ventriculaire provoqué par la compression oculaire, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 14, p. 739.

33. Petzetakis: L'épreuve paradoxale de l'atropine. Son action ralentissante sur le rythme cardiaque, Bull. et mém. Soc. méd. hôp. de Paris, 1914, No. 12, 567.

In this case the injection *slowed the pulse* and permitted the appearance of the reflex, which had not been present before. In most instances diagnoses of the disorders of the heart mechanism were made by means of polygraphic tracings. This method does not give conclusive information on some points of cardiac arhythmias, and when the tracings are made from patients disturbed by manipulation, they involve some doubt.

Pressure over the vagus nerves in the human subject has been studied particularly by Robinson and Draper.<sup>34</sup> They found that vagal pressure caused slowing of the auricles and ventricles and depressed conductivity in cases having normal hearts. The *Q-B* interval, i. e., the time between the *Q* wave in the electrocardiogram and the footpoint of the brachial pulse, was sometimes diminished. The right vagus had a greater effect on the force and rate of the heart, while the left vagus had a more pronounced effect on the conduction of impulses from auricles to ventricles. The heart was found to respond more quickly to right than to left vagal pressure. Right vagal pressure caused an increase in the action current of the ventricles and a decrease of the current of the auricles, i. e., the height of the *R* waves was increased and the height of the *P* waves was diminished. Left vagal pressure diminished the height of the *R* waves, while the *P* waves were unaffected. In cases of auricular fibrillation, vagal pressure slowed the ventricles without affecting the auricles. Reference will later be made to these results.

#### METHOD

In this investigation, patients were placed in the galvanometer circuit, and electrocardiograms were made to serve as controls. An assistant at the bedside, in continuous telephonic communication with the operator at the galvanometer, exerted pressure on the neck, or on the eye, as the case might be. Enough pressure was exerted on the neck entirely to obliterate the carotid pulse. No accurate measurement of the degree of pressure exerted on the eye was possible. An attempt was made later to determine the amount of pressure, in millimeters of mercury, used on the eyes in order to obtain a standard for comparison with other observers. As nearly as could be judged, a similar degree of pressure was applied to the distended air-tight bag of a blood-pressure apparatus. By this method the pressure employed was found to be approximately 30 mm. of mercury. The eyelid was first closed and the

34. Robinson, G. C., and Draper, G.: Action of Vagus Nerve on Human Heart, Jour. Exper. Med., 1911, xiv, 217; Studies with the Electrocardiogram on the Action of the Vagus Nerve on the Human Heart, Jour. Exper. Med., 1912, xv, 14.

operator's thumb applied under the supraorbital ridge, but not directly over the cornea. The pressure on the two eyes was made as nearly equal as possible. Before pressure was made a strip of curve of seven or eight seconds duration was taken. A signal registered the onset of pressure on the tracings. Pressure continued for about six or seven seconds, the offset being marked by the second signal in the tracing. The exposure was continued about eight or ten seconds longer to include the return of the heart's action to normal. In most cases the second lead was taken (right arm to left leg), but in some instances the first lead (right arm to left arm) was tried, to obtain, if possible, more prominent auricular waves.

Pressure was usually made first on the right vagus, then on the left vagus, then on the right eye and last on the left eye. Two records of each pressure (eight in all) were obtained. Four minutes were permitted to elapse between any two pressures, in order to exclude the summed influence of one on the succeeding. Occasionally, the left vagus was pressed on first and sometimes the left or right eye, to be certain to exclude confusion occasioned by fatigue phenomena. The same patient was in a few instances examined on two different days, and the order of pressure was reversed. Different degrees of pressure were used in the same patient at different times in order to determine whether the amount of slowing varied with the intensity of the pressure. Finally, the symptoms of the patient during pressure were recorded. The signs found included flushing of the face, inhibition of respirations, expressions of pain and the movements of deglutition, etc.

#### PROTOCOLS<sup>35</sup>

CASE 1.—Schoolboy, aged 9 years. He had a rheumatic history. Pupils react normally.

Clinical Diagnosis: Chorea, rheumatic fever, chronic valvular disease.

CASE 2.—Schoolboy, 11 years old. Pupils react normally.

Clinical Diagnosis: Chronic endocarditis.

CASE 3.—Clerk, 49 years old. No rheumatic history. Pupils react normally.

Clinical Diagnosis: Rheumatic fever, myocardial insufficiency, auricular fibrillation.

CASE 4.—Printer, 49 years old. No rheumatic history. Pupils equal, oval and react sluggishly to light. Reaction to accommodation is greater and more rapid.

Clinical Diagnosis: Talies dorsalis.

CASE 5.—Business man, 38 years old. Pupils are equal and react sluggishly to light. Both react well in accommodation.

Clinical Diagnosis: Syphilitic aortitis and syphilis of the spinal cord (syphilitic myelitis).

<sup>35</sup> The protocols have been compiled to report the sex, age, occupation, previous diseases having a possible influence on the cardiovascular system, the state of the pupils at the time of examination, and the clinical diagnosis.

CASE 6.—Male, 49 years old. Instructor in physical culture. Pupils are equal, small, do not react to light, prompt reaction in accommodation.

Clinical Diagnosis: *Tabes dorsalis*.

CASE 7.—Coachman, 45 years old. Pupils unequal, right is 2 mm., left is 5.5 mm. in diameter. Neither reacts to light and both have sluggish reaction in accommodation.

Clinical Diagnosis: Syphilis of the brain and spinal cord (probably early paresis or taboparesis).

CASE 8.—Salesman, 46 years old. Pupils unequal, right slightly larger than left. Both irregular. React slightly but sharply to light and normally in accommodation.

Clinical Diagnosis: *Tabes dorsalis*.

CASE 9.—Blacksmith, 58 years old. Rheumatic fever four years ago. Hard chancre thirty years ago. Pupils react normally.

Clinical Diagnosis: Acute rheumatic fever, acute pericarditis, cardiac arrhythmia, transitory auricular fibrillation, serofibrinous pleurisy and latent syphilis.

CASE 10.—Laborer, 31 years old. Rheumatic fever seven years ago, and two attacks since. Pupils react normally.

Clinical Diagnosis: Chronic valvular disease.

CASE 11.—School girl, 11 years old. Had one attack of rheumatic fever. Pupils react normally.

Clinical Diagnosis: Chronic mitral regurgitation. \*Chronic cardiac hypertrophy and dilatation.

CASE 12.—School girl, 9 years old. Rheumatic fever five years ago. Pupils react normally.

Clinical Diagnosis: Acute rheumatic fever, chronic valvular disease, mitral regurgitation, aortic regurgitation and aortic stenosis.

CASE 13.—School boy, 12 years old. Pupils react normally.

Clinical Diagnosis: Chronic valvular disease, mitral regurgitation and stenosis, chronic cardiac hypertrophy and dilatation. †

CASE 14.<sup>36</sup>—Tailor, 30 years old. Right pupil larger than left. Reaction to light and accommodation is active in both eyes.

Clinical Diagnosis: Secondary syphilis, syphilitic periostitis of the frontal bone, periostitis of ulna; multiple, gonorrheal, periurethral abscesses.

CASE 15.—School boy, 14 years old. Rheumatic fever. Pupils react normally.

Clinical Diagnosis: Acute rheumatic fever and acute endocarditis.

CASE 16.—School girl, 11 years old. Chorea and rheumatic fever. Pupils react normally.

Clinical Diagnosis: Lobar pneumonia.

CASE 17.—Male, 9 years old. School boy. No history of rheumatic fever. Pupils react normally.

Clinical Diagnosis: Lobar pneumonia and empyema.

CASE 18.—Cloakmaker, 40 years old. Pupils slightly dilated and unequal. Left is 4.5 mm., right is 4 mm. in diameter. Both irregular and react in accommodation but not to light.

Clinical Diagnosis: *Tabes dorsalis*.

CASE 19.—Bookkeeper, 63 years old. No history of rheumatic fever. Pupils equal and react in accommodation but not to light.

Clinical Diagnosis: *Tabes dorsalis*.

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36. Case 14 has been omitted because he began to show signs of early tabes, although the oculocardiac reflex was present.



CASE 20.—Electrician, 32 years old. Pupils unequal. Right is twice the size of the left. Both react slightly to light and well in accommodation.

Clinical Diagnosis: *Tabes dorsalis*.

CASE 21.—Business man, 26 years old. Rheumatic history eight years ago. Pupils slightly irregular in outline but react normally.

Clinical Diagnosis: Secondary syphilis. Syphilis of cerebrospinal meninges.

CASE 22.—Girl, 17 years old. Machine operator. Pupils react normally.

Clinical Diagnosis: Diabetes mellitus.

CASE 23.—Man, 53 years old. Actor. Pupils are unequal; right 3 mm., left 2.25 mm. in diameter. Neither reacts to light, but both react in accommodation.

Clinical Diagnosis: *Tabes dorsalis*.

CASE 24.—Reporter, 34 years old. Pupils are equal, irregular in outline, react normally to light and in accommodation.

Clinical Diagnosis: Secondary syphilis, syphilis of the cerebrospinal meninges, syphilis of the auditory and facial nerves.

CASE 25.—Tailor, 53 years old. Pupils equal, slightly irregular, do not react to light; both react slightly in accommodation.

Clinical Diagnosis: *Tabes dorsalis*.

CASE 26.—Porter, 35 years old. Pupils react normally.

Clinical Diagnosis: Lobar pneumonia and lung abscesses.

CASE 27.—Boy, 18 years old. Factory hand. Pupils react normally.

Clinical Diagnosis: Lobar pneumonia.

CASE 28.—Salesman, 24 years old. Pupils react normally.

Clinical Diagnosis: Lobar pneumonia.

CASE 29.—Diamond cutter, 60 years old. Had syphilis thirty-eight years ago. Pupils are somewhat dilated. Left does not react to light as completely and quickly as right. Both react well in accommodation.

Clinical Diagnosis: Transient heart-block. Syphilis of the heart.

CASE 30.—Farm hand, 26 years old. Pupils react normally.

Clinical Diagnosis: Acute rheumatic fever, acute myocarditis, lobar pneumonia.

#### GENERAL RESULTS AND OBSERVATIONS

The material for this study consisted of eight cases of *tabes dorsalis*, one case of *taboparesis*, five cases of syphilis which were non-tabetic, nine cases of chronic endocarditis (having a normal rhythm), one case of chronic endocarditis with auricular fibrillation, five cases of lobar pneumonia, and one case of diabetes mellitus. The five non-tabetic syphilitics included two cases of syphilis of the cerebrospinal meninges, one of syphilitic myelitis, one of syphilis of the heart, and one patient who has been observed during the secondary stage and who now suggests signs of early *tabes*.

The results of ocular and vagus pressure from four (Cases 4, 18, 20 and 25) of the eight cases of *tabes dorsalis* are shown in detail in figures 1a-d. Figure 1a gives the results of right vagus pressure, 1b of right ocular pressure, 1c of left vagus pressure and 1d of left ocular pressure. In one instance (Figure 1c, Tracing 157) there is marked slowing on vagus pressure. The degree of inhibition of the heart produced by vagus pressure was greater in this case than in any of the

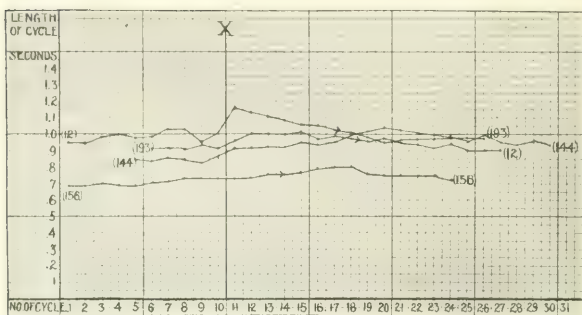


Figure 1a

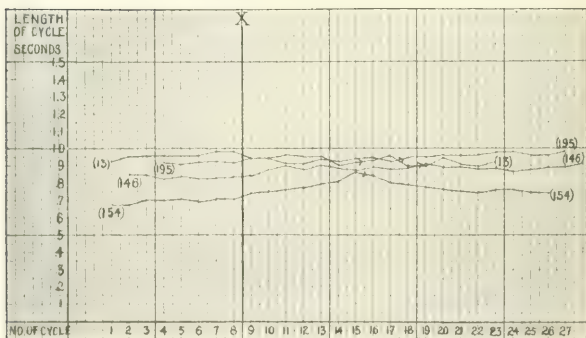


Figure 1b

Figures 1, 2, 3 and 4 detail the duration (on the ordinate) of every cardiac cycle (on the abscissa) calculated from electrocardiograms taken during a given digital (vagal or ocular) pressure. X indicates the onset of pressure; the arrow ( $\rightarrow$ ) the time of the offset. The figures marked *a* show the results

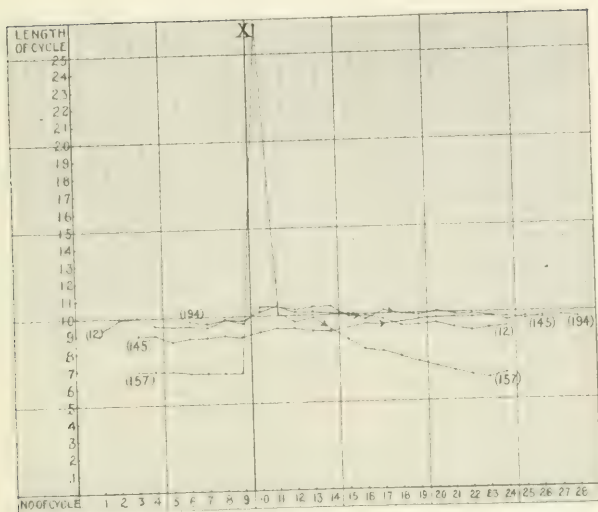


Figure 1c

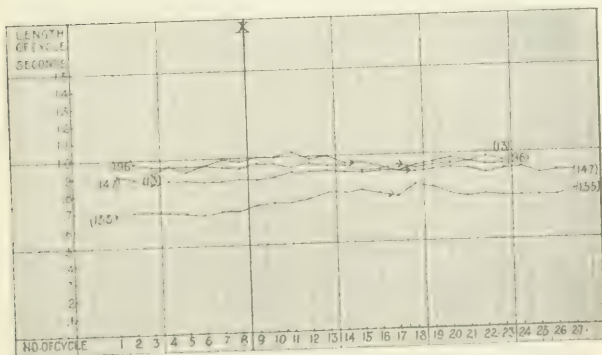


Figure 1d

of right vagus pressure, c, right ocular pressure, d, left vagus pressure, e, left ocular pressure. The numbers at the beginning and ends of the curves indicate, in the accompanying table, the patients to whom the curves refer.

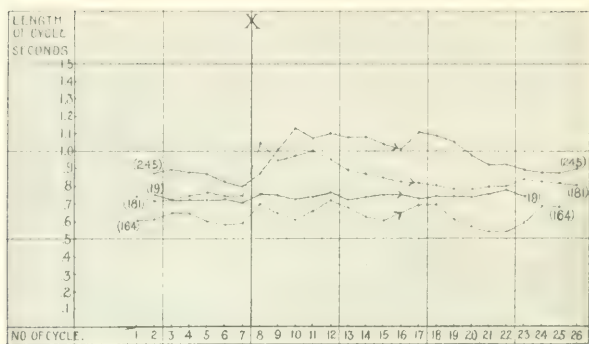


Figure 2a

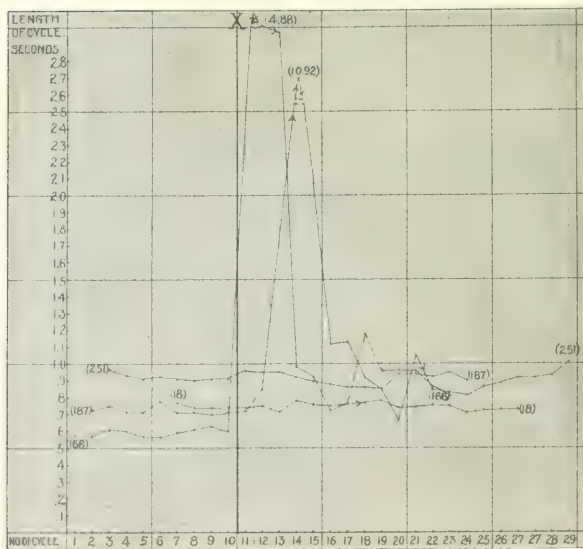


Figure 2b

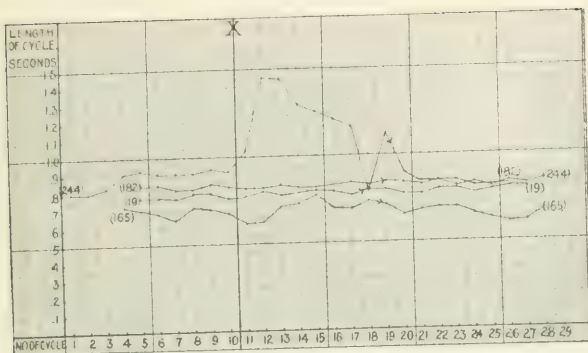


Figure 2c

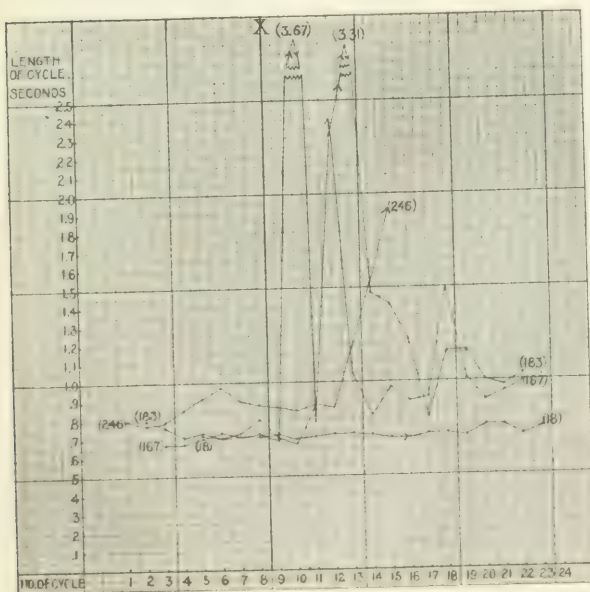


Figure 2d

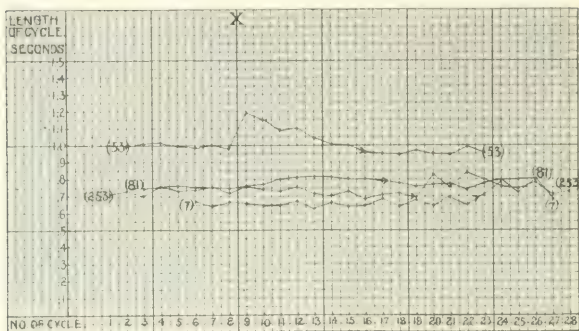


Figure 3a

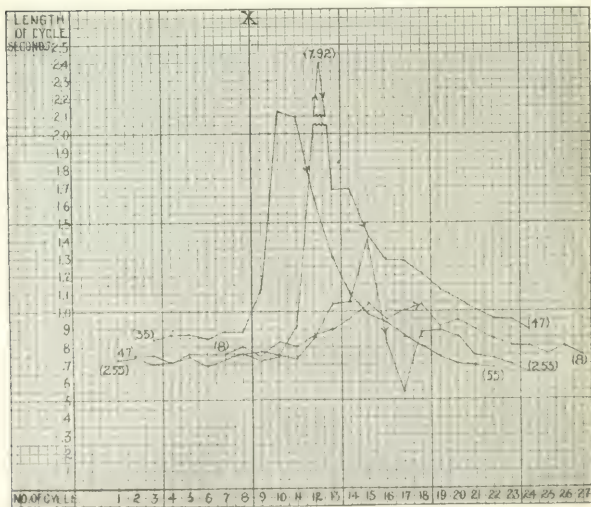


Figure 3b



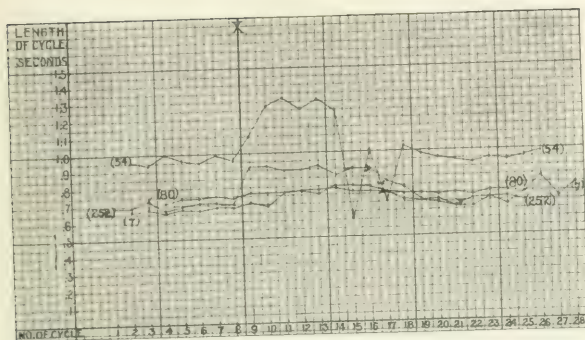


Figure 3c

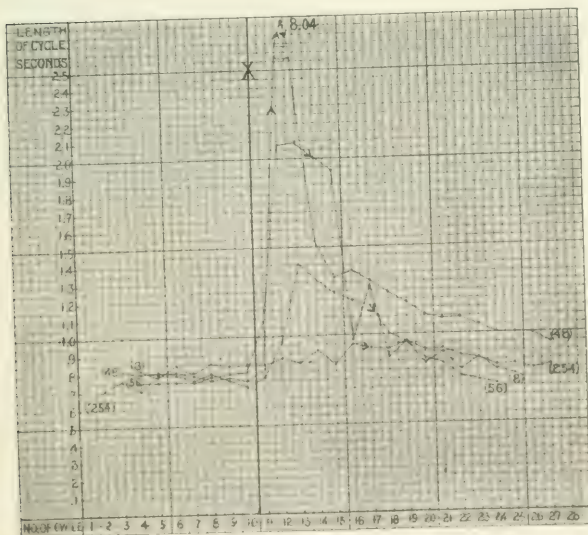


Figure 3d

other cases (tabetic or non-tabetic.)<sup>37</sup> This is a significant point, because although the oculocardiac reflex will be shown to be generally absent in tabetics and present in non-tabetics, the greatest degree of slowing by direct vagal pressure was obtained in a tabetic. The centrifugal path of the reflex was intact. One (Case 6) of the tabetics, whose pupils were rigid and did not react to light, developed a moderate amount of slowing as a result both of right and left ocular pressure. In some of the other tabetics, where the oculocardiac reflex was absent, the pupils reacted slightly to light. All the other tabetics gave no slowing on ocular pressure. In eight cases of *tabes dorsalis*, then, one showed a moderate oculocardiac reflex whereas it was absent in the other seven. There is, also, no exact parallelism between the Argyll Robertson reaction and the oculocardiac reflex. There was no

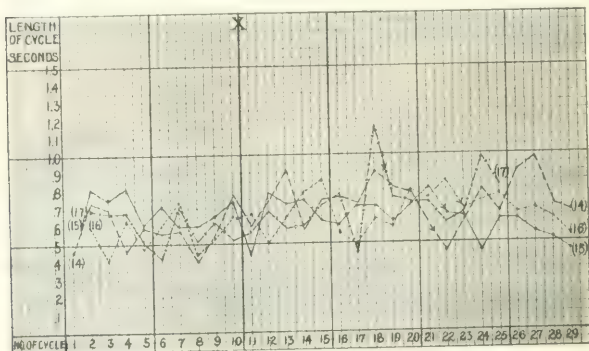


Figure 4a

Figure 4.—a and b give the results of pressure in a case (No. 3) of auricular fibrillation, before (a) and during (b) the administration of digitalis: a 14 + b 201 ——— right vagus; a 15 + b 208 ——— right eye; a 16 + b 202 - - - - left vagus; a 17 + b 209 x—x—x left eye.

difference in the effect produced by pressure on the two eyes. The only change noticed in the electrocardiograms was a slight increase in the prominence of the *P*-waves in two instances on right vagal pressure. There was no marked change in the conduction time or in the form of the ventricular complex.

In the second group of cases are included the four *syphilitics*<sup>38</sup> who were *not tabetic*. (Figs. 2a-d.) In three of the four cases, the oculo-

37. The term non-tabetic is used throughout to include all the cases in the series except those of *tabes dorsalis*.

38. Case 14, originally included here, has been omitted because he began to show signs which may be those of early *tabes*, although the oculocardiac reflex was present.

cardiac reflex was preserved. The results obtained here differ, therefore, from those obtained by Loeper, Mougeot and Vahram.<sup>19</sup> They found that in 75 per cent. of their cases of syphilis the oculocardiac reflex was *absent*. The reflex was *present* in 75 per cent. of the cases in this study. In two (Cases 21 and 24) of the four cases (Fig. 2b, Tracings 166 and 187, and Fig. 2d, Tracings 167 and 183) there was complete inhibition of the heart for periods ranging from 3.31 seconds to 10.92 seconds (Fig. 5). In a third case (No. 29) there was a moderate amount of slowing, that is to say, a slight reaction. The fourth (Case 5) did not react at all to ocular pressure. This case was one of syphilis of the spinal cord and syphilitic aortitis. He showed an Argyll Robertson pupil, so that it is not at all unlikely that he had early tabes. The slowing in these cases was more pronounced during pressure on the right

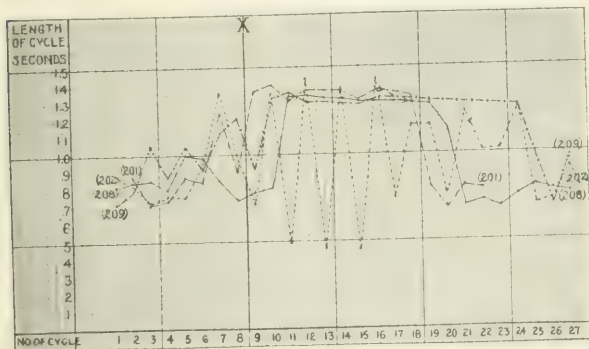


Figure 4b

ocular bulb than on the left. There were no changes in the electrocardiograms. In Case 21 an escaped ventricular beat occurred 0.79 second after the preceding pause of 3.67 seconds. Another long pause of 2.40 seconds followed. The escaped ventricular beat was of normal form, probably supraventricular in origin. In this case all the waves were greatly diminished in height during ocular pressure, so that it was difficult to differentiate a ventricular contraction from the oscillations that are sometimes observed in electrocardiograms during stimulation of the vagus nerves. Case 24 was very sensitive to ocular pressure. The pacemaker was entirely inhibited by right ocular pressure for 10.92 seconds (Fig. 5). Auriculoventricular conduction was lengthened considerably during pressure on the left eye. The effect on conduction, however, was not limited to pressure on the left eyeball, for the P-R time following the pause of 10.92 seconds was 0.24 second.

The results of vagal and ocular pressure were also studied in five cases of *pneumonia* (Cases 17, 26, 27, 28, 30). The curves plotted from electrocardiograms taken during vagal pressures rose very slightly, that is to say, pressure did not slow the heart very much. The curves of ocular pressure, on the other hand, rose abruptly after a latent period of from one to three beats. This demonstrates strikingly how much more effective ocular pressure is in slowing the heart than direct vagal pressure. Another point to be observed is that the pulse rate did not drop back to normal after pressure was released, but in fact was still quite slow after ten seconds, and in some instances after thirty seconds. This occurrence emphasizes the importance of waiting between succeeding pressures on the same patient, to guard against either fatigue phenomena or summation of stimuli. One of the pneumonia patients, Case 17, showed only slight slowing. The reason for this is, probably, that not enough pressure was exerted.

Three (Cases 17, 28 and 30) of the five pneumonia cases showed no changes in the form or sequence of the curves, except the slowing. In the other two, several interesting changes were observed. In Case 26 left ocular pressure caused considerable delay in conduction time. In places auricular waves cannot be distinguished at all, and yet the ventricular complexes are of normal contour. The auricular representation is iso-electric.

The last of the pneumonia cases (No. 27) presented varied changes during ocular pressure. Figure 8 shows three inverted *P*-waves, one of which was blocked. (Inverted *P*-waves were seen in one other instance during left ocular pressure.) The same tracing showed a conduction time of 0.28 second. On five different occasions left ocular pressure caused delayed conduction, the *P-R* interval rising to 0.24 and 0.32 second. In none of the four times when the right eye was pressed in this case was there any delay in conduction. Figure 6 shows partial heart-block as a result of left ocular pressure. Finally, in one instance, pressure on the left bulb caused an increase in the height of the *P*-waves, an occurrence observed also by Robinson and Draper<sup>34</sup> as a result of direct pressure on the left vagus nerve. In this case, then, right ocular pressure merely slowed the heart and had no effect on conduction. Pressure on the left eye, however, caused ectopic auricular contractions, delayed conduction, partial heart-block, and an increase in the height of the *P*-waves. These different effects appeared in the same individual under similar circumstances. It seems reasonable to believe that the duration and the force of the pressure, which must have varied, were important factors in determining the degree of inhibition that took place. Just as increasing strengths of faradic currents applied

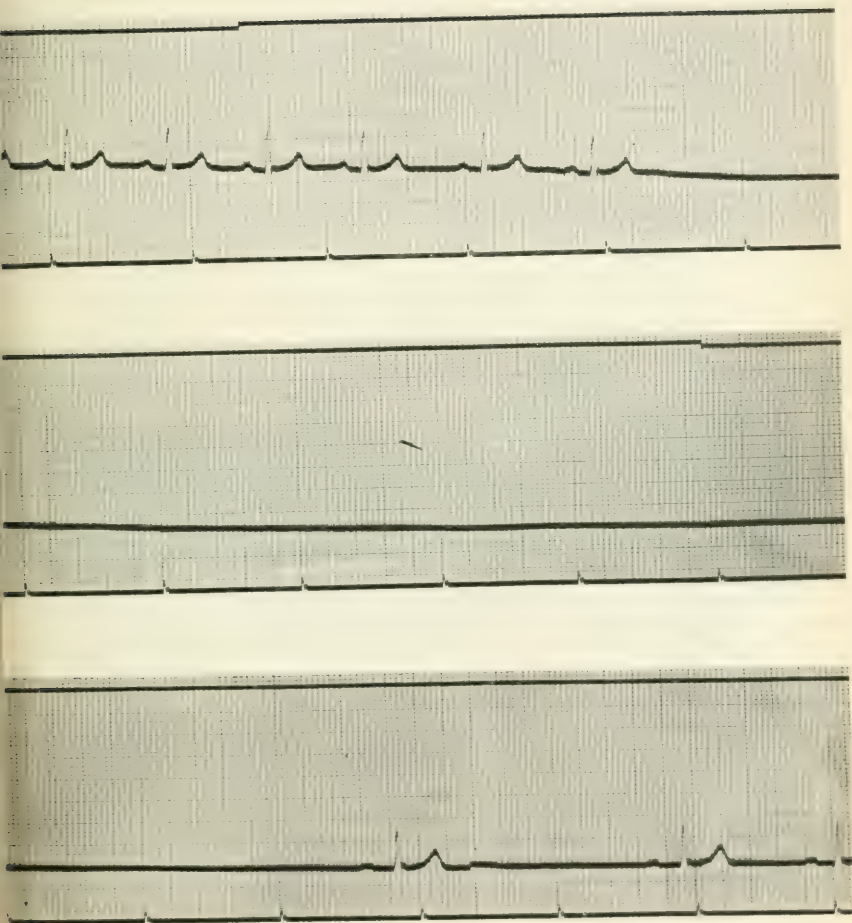


Fig. 5.—Case 24. Right ocular pressure. An electrocardiogram showing total inhibition of all chambers of heart for 10.92 seconds. The *P-R* time of the beat after the long pause is lengthened to 0.24 second. The slowing continued for twenty-four seconds after the release of pressure. In all curves, divisions on the abscissa equal 0.04 second. Above is a signal indicating the duration of digital pressure. Below a time scale marking one-second intervals.

to exposed nerves in experiments on animals are accompanied by increasing effects, so may increasing pressures produce increasing effects on the rate and on conduction. Mild pressures may slow the rate and perhaps slightly affect conduction; slightly greater pressures may block auricular beats, and great pressures may stop the heart. Under certain circumstances, possibly during removal of the pressure, complete auriculoventricular dissociation might occur. It is therefore important to standardize the degree and duration of pressure. In addition, the resistance offered by the eye is probably a factor involved in eliciting the reflex.

Nine cases of *chronic valvular disease* (Patients 1, 2, 9, 10, 11, 12, 13, 15, 16), all of whom had hearts actuated by a normal rhythm, were studied. Figures 3a-d show the results in four of them (1, 2, 9 and 10). Only one (Case 10) of the nine cases had a moderate reaction to *vagal pressure*, while another (Case 1) showed a slight effect. All the others were little, if at all, affected by either right or left vagal pressure.

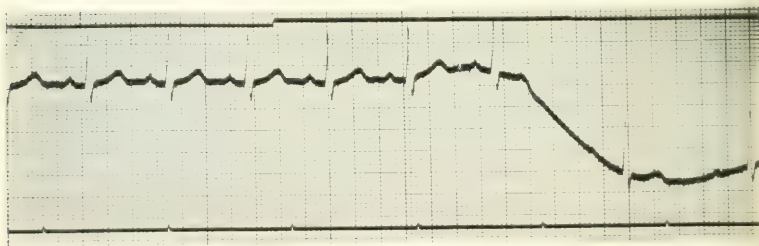


Figure 6

Fig. 6.—Case 27. Left ocular pressure. Moderate slowing of the heart is shown. There is a decrease in the size of the *P* wave. Conduction time is delayed and is gradually increased until an auricular beat is blocked. The *P-R* interval following the blocked beat is short, 0.15 second.

On *ocular pressure*, eight (Nos. 1, 9, 10, 11, 12, 13, 15 and 16) reacted strikingly, and the other one (No. 2) moderately. The patient (No. 2) who reacted with moderate slowing was not pressed very vigorously; he was one of the first patients studied. The first (No. 1) patient studied showed no slowing whatever on moderate ocular pressure, but on greater pressure he had a good reaction. In this case *P*-waves diminished in height during right ocular pressure, and during left ocular pressure *P*-waves were blocked. Left ocular pressure caused delayed conduction (*P-R* interval 0.44 second in one instance). Right vagal pressure caused a slight delay in conduction on one occa-



sion. There was no noticeable difference on the heart rate between the effects of right and left ocular pressure in these cases.

The results observed in one patient (Case 3) whose heart showed the rhythm of *auricular fibrillation* are included in the study. Observations were made before and during the administration of digitalis. Figure 4a shows the results of ocular and vagal pressures before digitalis was given. There was no evidence of slowing during pressure. Figure 4b, which gives the results after a course of digitalis therapy, shows a distinct slowing on pressure. There was no difference in effect between the right and left sides or between ocular and vagal pressure either before or during digitalis treatment. All other non-tabetic cases showed a distinct difference in reaction between ocular and vagal pressure. Many of them manifested differences in the effect of pressure on the right and left eyes. But here the result was the same whether ocular or vagal pressure was exerted or whether it was the left or right side that was used. The up and down swings in Figure 4b, Curve 202,

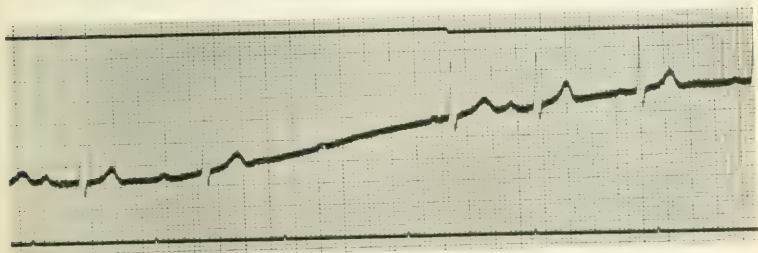


Figure 6—Continued

are due to three premature ectopic ventricular beats alternating with the normal ventricular contractions. There is a striking tendency for all normal heart cycles in this chart to be of the same length during pressure. Digitalis, it seems, changed the condition of the oculocardiac reflex. Wenckebach<sup>39</sup> and v. Hoesslin<sup>40</sup> have similarly shown that digitalis produces a heightening of the efficiency of vagus pressure.

One case of diabetes mellitus was studied (Case 22). Tracings were taken two different times at an interval of fifteen days. At neither time was there more than the slightest slowing either during vagal or ocular pressure. There has been no report in the literature of the condition of the oculocardiac reflex in this disease. A study

39. Wenckebach, K. F.: *Die Unregelmässige Herztätigkeit und ihre klinische Bedeutung*. W. Engelmann, Leipzig and Berlin, 1914, p. 172.

40. Von Hoesslin, H.: *Beobachtungen über den Einfluss des Vagus auf das menschliche Herz*. *Deutsch. Arch. f. klin. Med.*, 1914, cxiii, 537.

of more cases is required to decide whether the condition of the reflex found in this case is typical.<sup>41</sup>

The sensations experienced and the objective signs displayed during pressure have been studied to determine if differences between tabetics and non-tabetics were present, and to see if they were constant. Of the thirty patients studied, six had unusual sensations of one kind or another (Table 1). The others felt nothing but the pressure and the pain, when there was any. An examination of Table 1 shows that *vagus pressure* had little effect on either tabetics or non-tabetics. Occasionally a patient complained of slight pain; very rarely there was flushing or inhibition of respiration; on a few occasions the patient swallowed during or immediately after pressure. Deglutition might very well have resulted from the discomfort of the pressure on the neck. *Ocular pressure*, on the other hand, produced a marked difference in the two groups of cases. In the tabetics, three<sup>42</sup> had a moderate amount of pain (marked +), three had a slight or very slight pain (marked v. sl.) and three had no pain whatever (marked —). In five cases there was slight flushing and in four none at all. Respiration was checked during pressure on only two occasions and at no time was there any impulse toward swallowing. In contrast to this are the results in non-tabetics. The pain from ocular pressure was quite severe in all but two cases. One of these was a case of syphilitic myelitis (there is evidence that he is developing tabes), and the second was subjected to much lighter pressure than any of the others. There was flushing of the face in all but two cases. Respiration was checked in fifteen of the twenty cases. It is evident that pain, flushing of the face and respiratory inhibition generally occur during ocular pressure in non-tabetics, and to a much less extent in tabetics.

#### DISCUSSION AND SUMMARY

The oculocardiac reflex (inhibition of the heart produced by ocular pressure) is a normal but variable reflex. The statement that a heart is abnormal if its rate is slowed or accelerated by more than ten beats a minute, made by Loeper and Mougeot<sup>5</sup> is not substantiated by the observations made in this study. Some individuals normally have a more active oculocardiac reflex than others, just as some have more active tendon and superficial reflexes. In fact, when the reflex is con-

41. Since these observations were made, three cases of diabetes in the medical wards of the Peter Bent Brigham Hospital were investigated. In one case the oculocardiac reflex was absent on two different occasions. In the other two there was a moderate slowing on right ocular pressure, but none on the left.

42. I have included under tabetics Case 7, which is probably a case of early tabo-paresis.

TABLE 1.—SENSATIONS ELICITED BY PRESSURE IN TABETICS AND NON-TABETICS

TABETICS									
Vagus					Eye				Subjective Symptoms
Case	Pain	Flushing	Inhibition of Respiration	Deglutition	Pain	Flushing	Inhibition of Respiration	Deglutition	
4	—	+	—	+	+	sl.	—	—	Felt slight pain with ocular pressure, especially right.
6	—	—	—	—	—	—	—	—	Felt nothing but the pressure. No pain.
7	—	—	—	—	+	—	—	—	Slight pain in eyes. Pins and needles sensation in right eye.
8	—	—	—	—	—	—	—	—	Had no other feeling than that of pressure.
18	—	—	+	—	—	sl.	—	—	Merely felt pressure.
19	—	—	—	—	sl.	sl.	+	—	Merely felt pressure.
20	—	+	—	—	+	sl.	—	—	Pressure on left vagus made him feel faint.
22	—	—	—	—	vsl.	—	—	—	Felt nothing except slight pain in eyes.
25	—	—	—	—	sl.	sl.	—	—	Felt very slight pain in the eyes.
NON-TABETICS									
1	—	—	—	—	+	+	—	+	Pain in the eyes.
2	..	..	..	..	..	..	..	..	No record obtained.
3	—	sl.	—	—	++	+	—	—	Felt faint, choking sensation, cramp in belly when eyes were pressed.
5	—	—	—	—	—	—	—	—	Felt nothing peculiar. (See protocol.) (May be tabetic.)
9	—	+	—	—	++	+	+	—	Felt nothing but pain from pressure on eyes.
10	—	—	—	—	++	+	+	—	Felt nothing but pain from pressure on eyes.
11	—	—	+	—	++	—	+	—	Felt nothing but pain from pressure on eyes.
12	—	—	—	—	++	+	+	—	Felt nothing but pain from pressure on eyes.
13	+	—	+	—	++	+	+	—	Felt nothing but pain from pressure on eyes.
14	—	—	—	+	++	+	+	—	Felt nothing but pain from pressure on eyes.
15	—	—	—	—	++	+	+	—	Felt nothing but pain from pressure on eyes.
16	—	—	—	—	++	+	+	—	Felt nothing but pain from pressure on eyes.
17	—	—	—	—	++	+	+	—	Felt nothing but pain from pressure on eyes.
21	rt.	rt.	—	—	++	+	+	—	Felt nothing but pain from pressure on eyes.
22	—	sl.	—	—	++	+	+	—	Felt nothing but pain from pressure on eyes.
24	—	—	—	—	++	+	+	—	Felt slow electric current going through body when eyes were pressed. It caused him much pain.
26	—	—	—	—	++	+	+	—	Left eye pained more than right.
27	—	—	—	—	++	+	+	—	Left eye pained more than right.
28	—	—	—	—	++	+	+	—	Felt nausea when right eye was pressed, in addition to pain.
29	—	—	—	—	++	+	+	—	Merely felt pain.
30	—	—	—	—	++	+	+	—	When right eye was pressed right leg felt dead and it lifted itself up from bed.

sidered absent there is often a slight inhibition of the heart, as is shown by a tendency for the curves in Figures 1b and 1d to rise during pressure. It seems highly probable that different effects may be produced in the same individual by changing the duration and the degree of ocular pressure. This is shown in several cases described in this investigation. The comparison which was instituted made it clear that inhibition of the heart could much more easily be obtained by ocular than by direct vagal pressure. A difference as striking as that which has been observed between the two can only be obtained if the eyes are pressed quite firmly, causing the patient slight distress. Ocular pressure brings out disturbances in the heart mechanism which were not obtained by direct vagal pressure.

The reflex was found to be generally absent in *tabes dorsalis*. The cause for this probably is a lesion in the brain itself. Although in all the cases of *tabes* the pupils were inactive to light or reacted sluggishly,

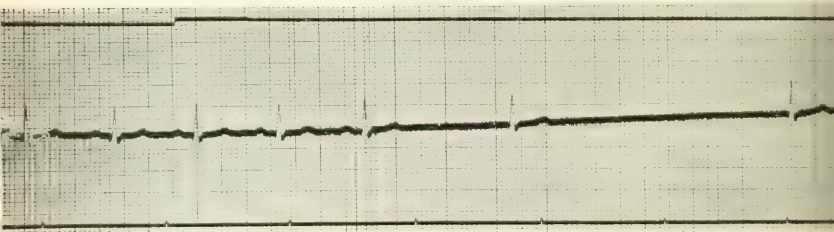


Figure 7

Fig. 7.—Case 26. Right ocular pressure. Total inhibition of the heart for periods of 2.27 seconds to 3.65 seconds is shown. *P*-waves are entirely absent; the ventricular complexes are of normal form. Beat V is an escaped ventricular contraction of normal form.

there does not seem to be any constant relation between the occurrence of the Argyll Robertson phenomenon and the loss of the oculocardiac reflex. In fact, the only tabetic who had a moderate oculocardiac reflex, had no pupillary reaction to light whatever. These findings in tabetics are in accord with the results obtained by previous investigators. Tabetics do not complain of pain on ocular pressure to the same extent as non-tabetics, nor do flushing of the face and periods of apnea during pressure occur to as great a degree as in non-tabetics. It is not impossible that these reflex phenomena result from the sensation of pain. Of the five cases of syphilis (Cases 5, 14, 21, 24 and 29), if those patients are excluded who might possibly be developing *tabes*, namely, Cases 5 and 14, then three, or 100 per cent., had a normal oculocardiac reflex; and if the other two are included, all but one, Case 5, or 80 per

cent., reacted normally. These results differ decidedly from those of Loeper, Mougeot and Vahram,<sup>49</sup> who found the reflex absent in 75 per cent. of their cases. One case of diabetes mellitus and one case of auricular fibrillation were found to have no oculocardiac reflex. No explanation for its absence can be given in the case of the diabetic. The patient with auricular fibrillation reacted after he was given digitalis. Of all the other cases in this series (including nine cases of chronic valvular disease, five of pneumonia, and five of syphilis) only one (Case 5) did not have an oculocardiac reflex, and he had signs of early tabes.

In tabetics there was no difference between the effects of pressure on the two eyes. In non-tabetics there was a distinct difference. The right reflex had a slightly greater effect on auricular contraction.<sup>43</sup> The different grades of inhibition caused by right ocular pressure were, first, a diminution in the height of the *P*-waves with only mod-

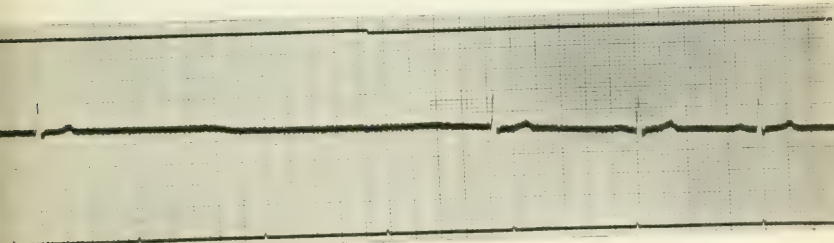


Figure 7—Continued

erate slowing; second, disappearance of the *P*-waves and slowing of the rate of the ventricular contractions; third, complete inhibition of all the chambers of the heart. Left ocular pressure, on the other hand, may cause similar phenomena, but does not do so as often as right. The *P*-waves frequently could not be identified, but after pressure was released they gradually reappeared (Fig. 7). The ventricular representative, *R*, continued to have a normal form even though the ventricular rate was reduced. It is impossible in these cases to say whether the normal pacemaker was completely inhibited or whether the origin of the impulse for ventricular contractions resided in the junctional tissue. In most instances the pacemaking function probably continued to be at the sinus node. In any case the impulse was supraventricular in origin, for the form of the ventricular complexes remained normal.

43. The greater slowing seen in the charts of pressures on the left side is only apparent and not real; it depends on the blocking of auricular beats which were slowed less by left than by right sided pressures. Rates, however, are counted from ventricular contractions.

The change in the mechanism of the heart beat caused particularly by left ocular pressure were delayed conduction, partial heart-block and inversion of the *P*-waves. Complete inhibition of all the chambers of the heart also occurred. Ectopic ventricular beats occurred in two cases during left ocular pressure. Accurate measurements of the heights of the *P*- and *R*-waves before and during ocular or vagal pressure were not made. *P*-waves diminished in height in many instances during both left and right ocular pressure. One case showed a decrease in the height of the *P*-waves even before slowing of the heart began.

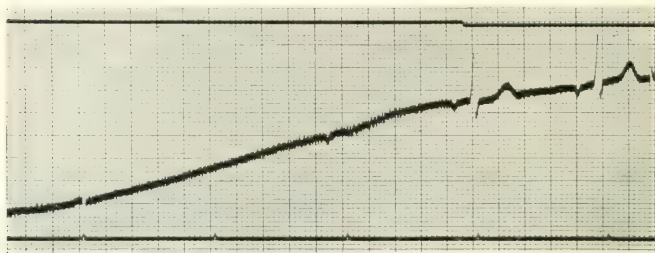


Fig. 8.—Case 27. Left ocular pressure. Inhibition of the ventricle is shown. Three inverted *P*-waves occurred one of which was blocked; in the other two the *P*-*R* time is short. After release from pressure the *P*-*R* time was 0.32 second.

Occasionally the height of the *P*-wave was increased by left ocular pressure.

Differences between right and left oculocardiac reflexes, such as were obtained by stimulation of the left and right vagus, were not as

TABLE 2.—PATIENTS REFERRED TO IN THE CURVES

Patient 4	Patient 18	Patient 20	Patient 25	Patient 5	Patient 21	Patient 24	Patient 29	Patient 2	Patient 10	Patient 9	Patient 1
Fig. 1a 12	144	156	193	Fig. 2a 19	164	181	245	Fig. 3a 7	53	81	253
b 13	146	154	195	b 18	166	187	251	b 8	55	47	255
c 12	145	157	194	c 16	165	182	244	c 7	54	80	252
d 13	147	155	196	d 18	167	183	246	d 8	56	48	254

definite and striking as those obtained in experiments by Cohn.<sup>44</sup> The fact that these differences were not so clearly demonstrated in the oculocardiac reflex must be due to the more complicated pathway pur-

44. Cohn, A. E.: On the Differences in the Effects of Stimulation of the Two Vagus Nerves on Rate and Conduction of the Dog's Heart, Jour. Exper. Med., 1912, xvi, 732.



sued by the impulses through the brain. According to the experiments referred to, the right vagus has a greater influence on the pacemaker and the left a greater influence on auriculoventricular conduction. The difference between pressure on the two eyeballs compares satisfactorily, however, with that found by Robinson and Draper<sup>34</sup> in their vagus experiments.

#### CONCLUSIONS

1. Ocular pressure affords a simple and safe method of obtaining reflex vagus inhibition of the heart.

2. Inhibition of the heart by the oculocardiac reflex is much more profound and more frequently obtained than by pressure over the vagus nerves.

3. The oculocardiac reflex is generally absent in tabes dorsalis, present in pneumonia, syphilis (non-tabetic) and chronic valvular disease.

4. The reflex was absent in one case of diabetes mellitus and also in one case of auricular fibrillation before digitalis treatment. It was present after digitalis was given.

5. Right ocular pressure has a slightly greater effect on the rate of the heart than left. It may stop the heart for a long period of time, relatively speaking, the *P*-waves are sometimes diminished in size and may become iso-electric. Occasionally the auriculoventricular interval is lengthened.

6. Left ocular pressure has a much greater effect on the conduction mechanism of the heart than right. It may lengthen auriculoventricular conduction, cause partial heart-block and result, possibly, in automatic ventricular rhythm. On two occasions inverted *P*-waves were seen. The height of the *R*-waves is sometimes increased, at other times diminished. Ectopic ventricular beats were twice observed. The *P*-waves are often diminished in size, but occasionally are increased. Escaped ventricular beats were seen both during right and left ocular pressure.

7. Pain, flushing of the face, and apnea during ocular pressure, are much less pronounced in tabetics than in non-tabetics.

8. The effects on the rate and on the rhythm of the heart produced by ocular pressures are not constant, differing in different individuals and in the same individual from time to time. The duration and the degree of pressure play an important part in the degree of inhibition.

I am greatly indebted to Dr. A. E. Cohn for his help and guidance throughout this investigation. I wish to express my thanks to Dr. Henry A. Christian for making this work possible.

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## COARSE AURICULAR FIBRILLATION IN MAN \*

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Faradic stimulation of the auricles of animals may produce any one or any combination of the following closely related conditions:

1. *Fine Fibrillation*.—This may be produced by auricular stimulation alone, but it is favored by simultaneous stimulation of the right vagus nerve.<sup>1</sup> During fine fibrillation the auricles appear dilated and motionless and from the mechanical point of view they may be said to be paralyzed. Close inspection, however, shows that they are the seat of numerous incoordinated contractions involving very small muscle bundles. It seems certain that this fine type of fibrillation produces no auricular venous waves of any magnitude.<sup>2</sup> On the other hand, changes in the electrical potential of different portions of the auricular musculature may cause distinct movements of the galvanometer string. The ventricles, being stimulated irregularly, take on a disorderly rhythm.

2. *Coarse Fibrillation*.—No sharp line separates this from the previous type and one may therefore speak of auricular fibrillation as being more or less coarse. When quite coarse the auricles can be seen to execute a series of very rapid, irregular contractions, which can be recorded by the myocardiograph.<sup>3</sup> These contractions differ from normal auricular systoles in that they are incoordinated. The entire auricle does not take part in each contraction, and at times wave-like peristaltic movements of the muscle may be seen. These auricular activities produce movements of the galvanometer string which are similar to, though usually coarser than those produced by the fine type of fibrillation. According to the experiments of Rothberger and Winterberg,<sup>4</sup> and of Lewis,<sup>5</sup> however, coarse electrical changes are not

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\* Submitted for publication Dec. 7, 1914.

\* From Department of Internal Medicine, University of Michigan.

1. Robinson, G. C.: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart. *Jour. Exper. Med.*, 1913, xvii, 429.

2. Rihl, J.: Ueber das Verhalten des Venenpulses bei Flimmern der Vorhöfe des Säugethierherens mit Rücksicht auf den Venenpuls beim Pulsus irregularis perpetuus, *Ztschr. f. exper. Path. u. Therap.*, 1910, vii, 693.

3. Winterberg, H.: Ueber die Wirkung des Nervus vagus und accelerans auf das Flimmern des Herzens, *Arch. f. d. ges. Physiol.*, 1907, cxvii, 223.

4. Rothberger, C. J., and Winterberg, H.: Ueber das Elektrokardiogramm bei Flimmern der Vorhöfe, *Arch. f. d. ges. Physiol.*, 1910, cxxxi, 387.

5. Lewis, T.: Auricular Fibrillation and Its Relationship to Clinical Irregularities of the Heart, *Heart*, 1909-1910, i, 306.

necessarily associated with coarse mechanical movements. As in the fine type of auricular fibrillation, the ventricles are stimulated irregularly and consequently take on a disorderly rhythm. The effect of such coarse auricular fibrillatory movements on the venous pulse seems variable. In Lewis' experiments the ventricular systoles caused the principal waves on the venous pulse. On the other hand, it seems probable from inspection of the auricular movements, from myocardiograph tracings, and from certain observations on the venous pulse,<sup>6</sup> that the auricular movements of coarse fibrillation may at times influence the venous pulse to a noteworthy degree.

3. *Auricular Tachysystole*.<sup>7</sup>—Rapid coordinated contractions of the auricles may occur as a result of faradic stimulation; particularly when, as in Robinson's experiments, the faradic stimulus is relatively weak and the electrodes are closely approximated. Auricular tachysystole is favored by simultaneous stimulation of the left vagus nerve. In Robinson's experiments the rapid auricular contractions were in most cases associated with fine fibrillatory movements of at least a portion of the muscle.

Observations on man have shown that these various types of irregularity produced by faradic stimulation of the auricles find their counterparts in clinical irregularities. Auricular tachysystole is characterized by an extremely rapid auricular rate (200 to 370 per minute).<sup>8</sup> Auricular waves are present on the jugular pulse and the ventricles usually respond to every second, third or fourth auricular beat. The string galvanometer shows a characteristic though abnormal deviation for each auricular systole, indicating that all have arisen from a definite region of the auricular muscle. The galvanometer records from man differ in this respect from those obtained by Robinson when auricular tachysystole was produced by faradization; for in the latter condition the deviations of the galvanometer string were much more irregular, possibly on account of the associated fibrillation. In man the intimate

6. Hewlett, A. W.: Auricular Fibrillation Associated with Auricular Extrasystoles, *Heart*, 1910, ii, 107.

7. In this article we have avoided the term "auricular flutter" because it seems to have been used to designate two separate conditions. Auricular flutter, as described by clinicians, is a condition in which very rapid, regular and coordinated auricular systoles arise from an abnormal but fixed region of the auricular muscle. This condition is called auricular tachysystole in the present article. Physiologists have used the term "flutter" to designate any coarse fluttering movements of the auricles. Some of these are manifestly closely related to fibrillation. In that sense the case here reported might be regarded as flutter; but we have preferred the term "coarse fibrillation," in order to emphasize the separation from clinical "flutter."

8. Ritchie, W. T.: Further Observations on Auricular Flutter, *Quart. Jour. Med.*, 1913, vii, 1.

relationship between tachysystole and fibrillation is shown, however, by the frequent passage of the one into the other.<sup>8, 9</sup>

Auricular fibrillation as observed in man usually causes rapid movements of the galvanometer string (400 to 500 or more per minute). In some patients these movements are distinctly coarser than in others. As has been pointed out, however, definite conclusions as to the coarseness of the mechanical movements of the auricles cannot be safely drawn from galvanometer records. Auricular fibrillation in man is almost invariably associated with a venous pulse of the ventricular type. Even during the long pauses that may intervene between ventricular systoles, there is rarely evidence of auricular activity. Only occasionally have small waves been encountered which may reasonably be attributed to the fibrillations;<sup>6, 10, 11</sup> but so far as we have been able to determine, these have always been insignificant when compared with the waves produced by the ventricular contractions. The following case is reported because the venous tracing was dominated by waves which were caused, as we believe, by an unusually coarse type of auricular fibrillation.

#### CASE REPORT

*History.*—J. K., a farmer, aged 47, entered the University Hospital April 22, 1914, complaining of shortness of breath. His family and personal history were unimportant. His present trouble began about six months before entering the hospital with dyspnea on exertion, which had persisted up to admission. He had also suffered from some precordial distress, both palpitation and pain. He had some cough and sputum, but had never had edema.

*Physical Examination.*—The patient was a well-nourished but slightly cyanotic man. The thorax was of the emphysematous type. It was hyperresonant on percussion, and a few crackles were heard at the bases. The cardiac impulse was diffuse, but most prominent in the fourth intercostal space in the mammary line. Although no marked change in cardiac dullness could be made out on percussion, the orthodiagraph showed a moderate enlargement of the heart shadow (142 sq. cm.). The heart action was very irregular. The sounds at the apex were clear, except for a slight systolic murmur after the longer diastolic pauses. The second sound was reduplicated over the pulmonary area. There was no edema and no enlargement of the liver. The larger pulse-beats came through the pressure cuff at a pressure of 150 mm. of mercury. The blood and urine were negative.

During his stay of ten days in the hospital the patient was treated with tincture of digitalis and the heart rate became considerably slower. Simultaneous venous and electrocardiographic records were taken on April 10, before admission to the hospital, and on April 24 and 30.

9. Robinson, G. C.: The Relation of Auricular Activity Following Faradization of the Dog's Auricle to Abnormal Auricular Activity in Man, *Jour. Exper. Med.*, 1913, xviii, 704.

10. MacKenzie, J.: The Interpretation of the Pulsations in the Jugular Veins, *Am. Jour. Med. Sc.*, 1907, cxxxiv, 12.

11. Wenkebach, K. F.: Beiträge zur Kenntnis der menschlichen Herztätigkeit, *Arch. f. Anat. u. Physiol., Physiol. Abth.*, 1907, i.

## THE GRAPHIC RECORDS

The electrocardiograms obtained differed in no essential particular from those frequently obtained from patients showing auricular fibrillation. The ventricular contractions, which occurred at irregular intervals, showed, as a rule, normal ventricular complexes which were interrupted here and there by abnormal complexes due to ectopic beats of ventricular origin. Normal P waves were absent, but throughout the tracings rather coarse vibrations of the string during diastole, such as occur in certain cases of auricular fibrillation, were present. These became particularly evident during the longer diastolic pauses of the slow heart-rate that developed during his stay in the hospital. These undulations occurred at the rate of about 450 per minute.

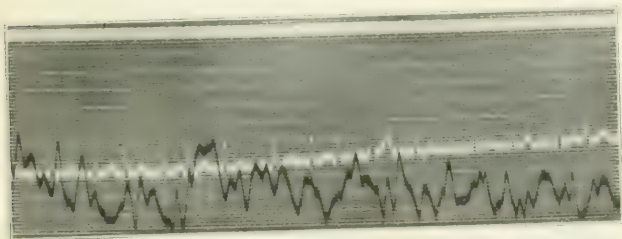


Fig. 1.—Electrocardiogram and venous pulse. Lead II (right arm and left leg). Sensitivity, 10 mm. equals 1 millivolt. Taken April 10, 1914, before treatment was begun. The ventricles are absolutely irregular. A single ectopic beat of ventricular origin occurs. The venous waves cannot be definitely correlated with the ventricular systoles.

Particular interest is attached to the venous tracings. Instead of a well-defined positive ventricular pulse, such as is commonly seen in auricular fibrillation, the venous waves occurred irregularly and were not readily correlated with the ventricular systoles. During the more rapid ventricular rate present in the earlier tracings the venous records were not readily analyzed (Fig. 1). When records were obtained during the slower heart action, however, it became evident that many of the venous waves which occurred during the latter portions of the long diastolic pauses could not possibly have been dependent on the contractions of the ventricles (Figs. 2, 3 and 4). They were neither stasis waves nor the *h* waves of Hirschfelder. They must have been due, therefore, to the activity of the auricles. We found, furthermore, that many of the unusually large waves during ventricular systole bore no definite or constant time relation to the systole itself (Figs. 2, 3 and 4). In our opinion, these waves were produced by auricular con-

tractions which occurred while the tricuspid valves were closed, being similar to the unusually high venous waves produced whenever auricles and ventricles contract simultaneously.

#### THE INTERPRETATION OF THE RECORDS

Since most of the prominent waves on our venous tracings were, as we believe, due to auricular activity, the question arises whether or not our case should be classed as one of auricular tachysystole. It resembled this condition in so far as rapid auricular contractions were recorded in the venous tracings. On the other hand, it differed in the following particulars: 1. The auricular contractions were not regular. 2. There was no constantly recurring auricular complex on the electro-

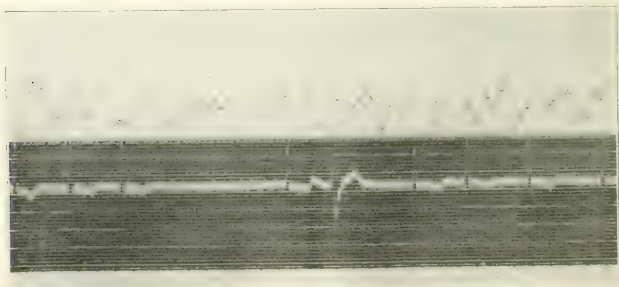


Fig. 2.—Electrocardiogram and venous pulse. Lead I (right arm and left arm). Sensitivity, 10 mm. equals 1 millivolt. Taken April 30, 1914, after treatment with rest and digitalis. The ventricles are absolutely irregular but beating at a slow rate with some very long diastolic pauses. The venous curve shows prominent waves during the long diastolic pauses.

cardiogram. 3. No definite relation existed between the waves on the electrocardiogram and those on the venous pulse. At times the venous pulse showed marked waves while the galvanometer string was comparatively motionless (Fig. 3). Furthermore, although the movements of the string and the venous waves had approximately the same rate of vibration, there was no definite time relationship between the two. The onsets or crests of the one set of waves bore no definite relation to the onsets or crests of the other. It seems evident, therefore, that we are not dealing, as in auricular tachysystole, with a series of rapid coordinated auricular contractions all of which arose from the same region of the heart, but with a series of irregular contractions of the auricles which, from their lack of relationship to the galvanometer curves, were apparently originating at different points and



progressing in different directions over the auricular musculature. The separation from tachysystole is also favored by the fact that the ventricular rhythm was absolutely irregular and that digitalis slowed the heart and atropin quickened it, not by sudden jumps from one rate to another, but by gradual changes in rate analogous to those produced when these drugs are given to patients suffering from the ordinary type of auricular fibrillation.

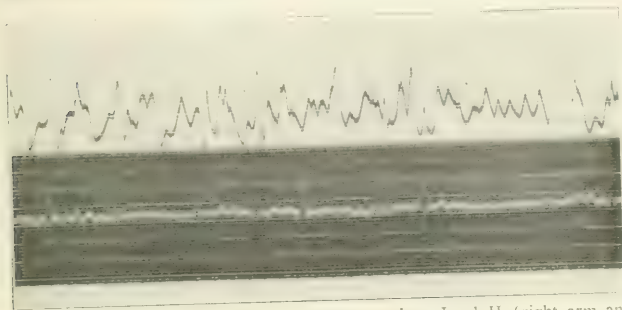


Fig. 3.—The electrocardiogram and venous pulse. Lead II (right arm and left leg). Sensitivity, 10 mm. equals 1 millivolt. Taken shortly after Figure 2, shows the same characteristics except that R is shorter, and coarser electrical waves are seen during certain diastoles. The venous waves during the systoles bear no definite time relationship to the electrical complexes.

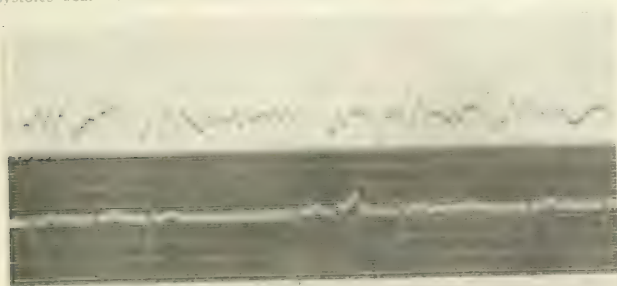


Fig. 4.—The electrocardiogram and venous pulse. Lead III (left arm and left leg). Sensitivity, 10 mm. equals 1 millivolt. Taken shortly after Figure 3; shows the same characteristics, except that the most prominent wave of the ventricular complex is in the opposite direction.

It seems to us, therefore, that both by exclusion and by direct analogy with animal experiments our tracings are best explained by assuming that the auricles were fibrillating in such a coarse manner that they produced marked venous waves. This hypothesis explains

the rapid auricular rate. The lack of correspondence between venous and galvanometer records is explained by the fact that in fibrillation the mechanical movements of the auricles and the differences in potential between two given portions of the auricular muscle are more or less dissociated on account of the local character of the contractions and the interference phenomena produced by the simultaneous occurrence of more than one partial contraction. The effects produced by digitalis and by atropin were those usually produced by these drugs during the ordinary type of auricular fibrillation.

A word should be said about the method of recording the venous pulse, and its possible relation to our records. In making venous records we used the usual receiving tambour and air transmission. A small mirror was pasted on the recording tambour and a beam of light projected from this mirror was photographed on the moving sensitized surface. The inherent vibration of the system was 25 to 40 per second, a rate much faster than that of the mechanical recorders commonly used for the venous pulse, and sufficiently fast for the accurate reproduction of all but the most sudden venous waves. It might be questioned whether, with this more accurate recorder, mechanical evidence of auricular fibrillation might not be more frequently obtained than is usual on venous records. We suspect that this may be the case, but in a limited experience with the method we have found that venous tracings from the other cases of auricular fibrillation examined showed no such prominent waves as in the case here reported. The waves cannot, therefore, be attributed to the method used, but are due to peculiarities in the activity of the auricles.

#### CONCLUSIONS

1. A case of continuous irregularity is reported in which the venous curves were characterized by numerous very rapid and irregular waves produced by auricular activity. These waves bore no definite relationship to the auricular fluctuations of the galvanometer string.
2. We believe the condition to be one of unusually coarse auricular fibrillation.

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## CLINICAL CALORIMETRY

### FIRST PAPER

#### A RESPIRATION CALORIMETER FOR THE STUDY OF DISEASE \*

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### HISTORICAL

A respiration calorimeter is an apparatus designed for the measurement of the gaseous exchange between a living organism and the atmosphere which surrounds it, and the simultaneous measurement of the quantity of heat produced by that organism.

The first contrivance of this nature was described by Lavoisier in 1780. It will be remembered that Lavoisier was the first to comprehend the significance of the then newly discovered oxygen. Primitive though the apparatus, yet intellectually inspiring was the mind which so early grasped the principles and understood many of the difficulties.

Apparatus for the measurement of the respiratory exchange was perfected before that for the measurement of heat production. Thus. Regnault and Riesel<sup>1</sup> in 1850 designed an air-tight apparatus in which an animal was placed; the carbonic acid formed in it was removed by pumping the air into flasks filled with potash, and oxygen was added from time to time as it was required. This is the *closed circuit* system which in a modified form is used to-day.

The historic respiration apparatus of Pettenkofer<sup>2</sup> and Voit was completed in 1862. This machine was capable of measuring the carbon dioxide output of a man within 1 per cent. of error. As early as 1866 Voit began computing from the substances oxidized in the body the quantity of heat which should have arisen from the destruction of those substances. This method is known as *indirect calorimetry*.

\* Submitted for publication Oct. 20, 1914.

\* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division of Bellevue Hospital.

1. Regnault and Riesel: Ann. d. Chem. u. Pharmakol., 1850, lxxiii, 92, 129, 257.

2. Pettenkofer: Ann. d. Chem. u. Pharmakol. Supplement 2, 1862.

In 1885, Rubner, working in Voit's laboratory, published results concerning the calorimetry of foods. Accurate determinations of the heat value of urea, and of dry urinary solids were made for the first time. This work established biological standards for the heat values of proteins, carbohydrates and fats which are to-day accepted.

About the same time a calorimeter for the measurement of the heat production in man was set up in Voit's laboratory and many experiments were made with it by Carl Voit and his brother Erwin Voit. The results were apparently not satisfactory, for nothing was ever published on the subject. At this time Atwater was in Voit's laboratory, and in 1888 published from that laboratory an article on the absorption of the flesh of fish.

Atwater's interest in nutrition had already been stimulated by Johnson and Brewer at Yale, and through studies in agricultural and physiological chemistry in Berlin in 1869-71. In 1877 he began investigations into dietary requirements of the people. It was Atwater's association with Voit and with Rubner, however, which gave him his knowledge of the principles of the subject of calorimetry as applied to the living organism. These facts, which are not widely known, emphasize again the overwhelming debt which American science owes to Germany.

In 1894 Rubner built the first successful respiration calorimeter. He built it largely with his own hands and with the very moderate means available in his laboratory at Marburg where he had become professor of hygiene. Voit, on hearing the news, said that it was the most important invention of its kind since the invention of the thermometer. Rubner's calorimeter, which measured the heat production of a dog, was associated with the mechanism of a Pettenkofer respiration apparatus which determined the carbonic acid output of the animal. Thus *indirect calorimetry* could be compared with *direct calorimetry*. For example, if the nitrogen in the urine and feces of a dog fed with meat and fat were determined, and this nitrogen were multiplied by 6.25, the quantity of protein destroyed could be estimated. Since each gram of protein yields 4.1 calories of heat in the body, the quantity of heat produced from protein would be

$$\text{Grams excreted N} \times 6.25 \times 4.1$$

To estimate the quantity of fat oxidized the quantity of carbon contained in the protein destroyed (which amounts to grams excreted  $\text{N} \times 3.28$ ) was deducted from the quantity of carbon contained in the

3. For the history of animal calorimetry see Rubner: *Tigerstedt's Handbuch der physiol. Methodik*, i, 150; Johansson, *Abderhalden's Handbuch der biochem. Arbeitsmethoden*, Berlin, 1910, iii, 1114.

excreta, that is, the sum of that in the urine, feces and respiration. The remainder represented the quantity of expired carbon derived from the oxidation of fat. Since fat contains 76.5 per cent. of carbon and 1 gm. of fat yields 9.3 calories, it was easy to calculate the heat production derived from fat. Recapitulating, one may express the heat produced from fat in the formula:

$$\text{Total C} = (N \times 3.28) \text{ divided by } 76.5 \times 100 \times 9.3$$

Adding together the heat calculated as that which should have arisen from the protein and fat metabolized, Rubner found that this sum was exactly the amount of heat given off by the animal as measured by the calorimeter. This was the first long-sought demonstration of the law of the conservation of energy applied to animal life.

After returning to America, Atwater in 1892 began work on a calorimeter which could measure the heat production in man. In 1894 the United States government began to appropriate funds for investigations into the nutrition of the people and placed the distribution of these funds in the hands of Professor Atwater. A portion was wisely used in the construction of the Atwater-Rosa<sup>4</sup> respiration calorimeter, the earlier description of which appeared in 1897. In 1893 C. F. Langworthy and in 1895 F. G. Benedict became associated with the undertaking. Shortly after the completion of the apparatus, Rosa, the expert physicist, to whose skill its successful completion was largely indebted, retired from direct association with the enterprise, although, as professor of physics at Wesleyan he was still frequently consulted until, in 1901, he became chief physicist of the Bureau of Standards at Washington. The Atwater-Rosa calorimeter demonstrated that direct and indirect calorimetry agreed in man, not only during rest, but also during periods when mechanical work was performed.

The original Atwater-Rosa calorimeter was associated with a respiration apparatus of the type designed by Pettenkofer, which measured only the carbon dioxide output. Calculated on this basis the production of heat might show a maximum error of 24 per cent., depending on whether carbohydrate or fat was being oxidized. At a later date funds were granted to Atwater by the Carnegie Institution in order to apply the principle of the closed circuit of Regnault and Riesel to the apparatus so that the oxygen absorption might also be determined. The modification of the apparatus along these lines was begun in 1902, and the work accomplished during 1903 to 1905 was done during a period when Atwater was in full control of the undertaking. Atwater's illness

4. Atwater and Rosa: Report of the Storrs Agric. Exper. Station, 1897, p. 212.

began in 1905, his retirement took place in 1906 and he died in 1907.

With the improved apparatus, publication<sup>5</sup> concerning which fell in 1905, not only heat production and carbon dioxid output were accurately measured, but the absorption of oxygen as well. It thus became possible to measure not only the non-protein carbon in the respiration, but also to calculate how much of the oxygen absorbed was devoted to the destruction of non-protein material; that is to say, fat and carbohydrate. The value of this knowledge becomes apparent when it is realized that one liter of oxygen used for the oxidation of fat yields 4.686 calories, whereas when the same volume is used to oxidize starch 5.047 calories are set free, a difference of over 7 per cent. When carbohydrate is oxidized the volume of oxygen absorbed is equal to the volume of carbon dioxid expired and the *respiratory quotient* equals unity.

$$\text{R. Q. equals } \frac{\text{Vol. CO}_2}{\text{Vol. O}_2} = 1$$

When fat is oxidized, however, the respiratory quotient is only 0.70. Respiratory quotients (corrected from protein influence) which run intermediate between 0.70 and 1.00 are deemed to represent the oxidation of mixtures of carbohydrates and fats, and the heat value of a liter of oxygen varies accordingly. Thus a quotient of 0.85 represents the oxidation of fat and carbohydrate together in such a proportion that 49 per cent. of the calories produced are derived from carbohydrate and 51 per cent. from fat. Under these circumstances, 1 liter of absorbed oxygen represents 4.863 calories liberated in the organism. Tables giving these data were first published by Zuntz.<sup>6</sup>

The ability to determine the oxygen absorption with exactness abolished a possible error of considerable magnitude in the calculations of indirect calorimetry. This improvement brought the apparatus to a high degree of perfection. The Carnegie Institution of Washington has richly provided for the higher development of the work in the Nutrition Laboratory at Boston, which represents the realization of Atwater's ambition for the establishment of a separate laboratory for this work. Dr. Benedict is here the controlling genius, while the original Wesleyan calorimeter, now removed to Washington, is under the direction of Dr. C. F. Langworthy.

5. Atwater and Benedict: Carnegie Institution of Washington, 1905, Pub. 42. See also, Benedict and Carpenter: 1910, Pub. 123.

6. Zuntz and Schumburg: Studien zu einer Physiologie des Menschen, Berlin, 1901. See also, Williams, Riche and Lusk (Jour. Biol. Chem., 1912, xii, 357), for other references.



ANIMAL CALORIMETRY AT THE CORNELL UNIVERSITY  
MEDICAL COLLEGE

At the time of my appointment to the professorship of physiology at the Cornell University Medical College, the authorities liberally provided for the construction of a respiration apparatus. Dr. Murlin spent a part of the summer with Dr. Benedict in Boston, where he freely received every privilege of the laboratory. After considerable discussion, I decided to have a calorimeter constructed which was small enough for use with dogs and babies, work which, up to that time, had not been included in the program of the Boston laboratory. The construction of this apparatus was entrusted to the capable management of Dr. H. B. Williams.<sup>7</sup> Full and grateful acknowledgment is due to Dr. F. G. Benedict, who has ever given all that counsel which his unique experience in calorimeter construction makes of highest value.

The problem of the measurement of 7 calories of heat produced in an hour by a baby weighing 3 kg. was different from that presented by the measurement of 70 calories produced by an adult. This led to the addition to the calorimeter of certain refinements in technical construction which are due to Dr. Williams. The small calorimeter has been successfully used in many experiments on dogs and babies. For the first time direct and indirect calorimetry were found to agree during hourly periods of experimentation.

The method employed with dogs was to determine the *basal metabolism* as measured by that quantity of heat which was produced by the resting animal when there was no food in the gastro-intestinal tract, and to compare this metabolism with that found at times following the ingestion of various foods. It was found that three or four hours of observation sufficed to indicate the influence of ingested food.

The satisfactory working of the apparatus used in accordance with these principles encouraged me to believe that valuable results might be obtained concerning the nutrition of patients if a similar, though larger, apparatus were placed in Bellevue Hospital. Before embarking on the undertaking, inquiry was made of Dr. Benedict if he did not desire to investigate this field by establishing a calorimeter in the Peter Bent Brigham Hospital in Boston. As the reply was in the negative, it appeared justifiable to seek money and opportunity for the accomplishment of this work.

Sufficient funds were obtained from the Russell Sage Institute of Pathology for a period of five years. The former arrangement between this institute and the City Hospital had just been terminated. A new arrangement was entered into with the trustees of Bellevue Hospital

7. Williams: Jour. Biol. Chem., 1912, xii, 317.

which enabled the institute to construct the first respiration calorimeter ever established in a hospital. Dr. Eugene F. Du Bois was appointed medical director, and the whole undertaking has enjoyed the faithful service of chemists, mechanics and nurses who have contributed to its success. A factor of especial encouragement has been the personal interest in the undertaking manifested by the visiting physicians, Drs. W. Gilman Thompson, C. L. Dana and Warren Coleman. The last-named has taken part in the actual work of the institute.

It is also a pleasure to acknowledge with thanks many helpful suggestions made by Drs. Langworthy and Milner of Washington.

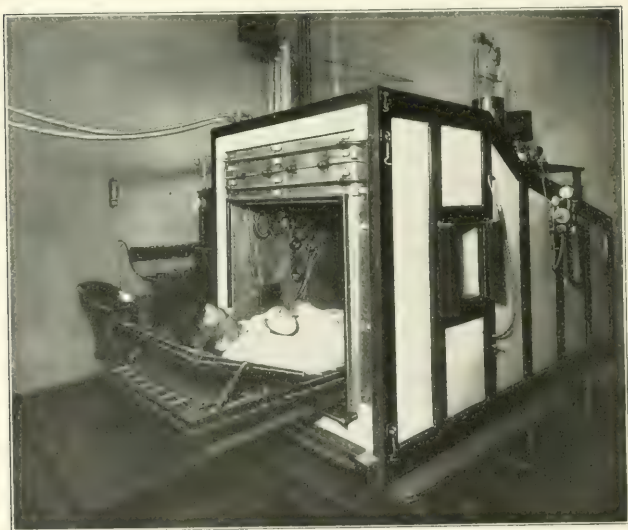


Fig. 1.—Respiration calorimeter with the patient half-way in. On his chest can be seen the tube of the Bowles stethoscope strapped over the heart. Coiled up on the wall is the rectal thermometer not yet inserted. Just below this is one of the units of the air thermometer and to the right is the telephone.

An Atwater-Rosa-Benedict respiration calorimeter, together with the instruments of precision applied to it by Williams, and certain new modifications which were the result of advice and experience, was established in Bellevue Hospital. The papers which follow are descriptive of the calorimeter (Fig. 1) and the results obtained with it. The patient lies quietly for three or four hours on a comfortable bed in the chamber of the apparatus, breathing the purest air, without the possi-

bility of harm. The long periods of the older respiration chambers and the nose- or mouth-pieces of the short-period apparatus are not disturbing factors. For the benefit of those who are interested in the work and who do not care to follow the details of the technical description of the apparatus, the following summary will suffice.

#### PRINCIPLE OF THE ATWATER-ROSA-BENEDICT RESPIRATION CALORIMETER

The apparatus is divided into two functional parts, one for measuring the gaseous exchange, the other for measuring the heat production of the subject. A schematic presentation is here given (Fig. 2).

*The Gas Analysis.*—The inner lining of the apparatus presents an air tight copper box having a capacity of 1.123 liters. One end of the box, through which the patient lying on the bed is admitted, may be closed with a glass-plate by means of wax. The air within the box is purified by drawing it out of an opening in the box through a rubber tube and forcing it by means of a rotary blower through a system of *absorbers*, whence it returns again to the box by another rubber tube. It passes (see diagram) first through sulphuric acid (1), which removes the water, then through moist soda lime (2), which removes the carbon dioxide, and next through sulphuric acid (3), which absorbs the moisture taken from the soda lime. If the bottles be previously weighed, the gain in weight of 1 represents water absorbed, and the gain in weight of 2 plus 3 equals the carbon dioxide absorbed. By this method the water and carbon dioxide produced by a man are taken from the air, while oxygen within the chamber is being absorbed by the man himself. This causes a diminution in the volume of the contents of the box. In order to replace the oxygen used, oxygen is automatically fed into the system from an oxygen cylinder which may be weighed before and after the period. The automatic feeding of oxygen into the box is accomplished by means of a spirometer whose interior is connected with the interior of the calorimeter chamber. As the volume of the air in the box decreases, the spirometer falls until a certain point is reached, at which an electric contact releases a clamp, which allows oxygen from the oxygen cylinder to enter the box, causing the spirometer to rise, break its electric contact and clamp off the oxygen supply. So sensitive is the spirometer to the movement of the patient that a device called a "work adder" has been attached to it, which records the subject's movements.

At the beginning of an hourly period of experimentation an observer at the table calls "time." At this instant the rotary blower is stopped, the air current switched so as to pass through a new set of weighed absorbers and then the rotary blower is started again. At the word "time" an operator also turns a pet-cock which cuts off the respiratory chamber from the spirometer cylinder, which is then filled, always to a given point, with oxygen from the oxygen cylinder. The pet-cock is now opened and a freshly weighed oxygen cylinder is placed in the position of the other, which is removed. Repeating these procedures an hour later, one may determine by difference in weight the gain of water and carbon dioxide by the absorbers and the loss of oxygen by the cylinder. The figures are subject to corrections due to (1) gain or loss of water or carbon dioxide content in the box itself, during the period, which gain or loss must be added to or subtracted from the increase in weight of the absorber system. This gain or loss of water and carbon dioxide in the box also affects the volume of the air in the box and, therefore, the quantity of oxygen admitted, as do, in addition (2), a change in temperature within the box and (3) a change in barometric pressure. These corrections must be made in order to determine whether oxygen is to be added or subtracted from the quantity which has been furnished from the oxygen cylinder. The result

gives the quantity of oxygen which the man has absorbed. It is apparent that all the errors of determination fall on the oxygen, and yet the exactness of the method is witnessed by the close approximation in alcohol check experiments of the theoretical and actual values for oxygen consumed.

If a person in the calorimeter moves even the arm during the critical moments just before "time" is called, the increased local heating of the air may cause the spirometer to rise to a considerable height, of which the air

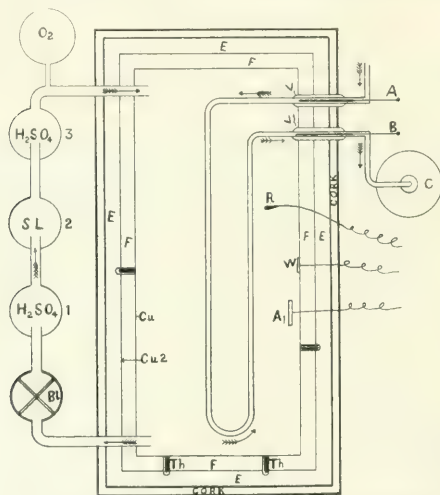


Fig. 2.—Schematic diagram of the Atwater-Rosa-Benedict respiration calorimeter.

#### Ventilating System:

- O<sub>2</sub>, Oxygen introduced as consumed by subject.
- 3, H<sub>2</sub>SO<sub>4</sub> to catch moisture given off by soda lime.
- 2, Soda lime to remove CO<sub>2</sub>.
- 1, H<sub>2</sub>SO<sub>4</sub> to remove moisture given off by patient.
- Bl., Blower to keep air in circulation.

#### Indirect Calorimetry:

- Increase in weight of H<sub>2</sub>SO<sub>4</sub> (1) = water elimination of subject.
- Increase in weight of soda lime (2) + increase in weight of H<sub>2</sub>SO<sub>4</sub> (3) = CO<sub>2</sub> elimination.
- Decrease in weight of oxygen tank = oxygen consumption of subject.

#### Heat-Absorbing System:

- A, Thermometer to record temperature of ingoing water.
- B, Thermometer to record temperature of outgoing water.

V, Vacuum jacket.

C, Tank for weighing water which has passed through calorimeter each hour.

W, Thermometer for measuring temperature of wall.

A1, Thermometer for measuring temperature of the air.

R, Rectal thermometer for measuring temperature of subject.

#### Direct Calorimetry:

Average difference of A and B × liters of water + (gm. water eliminated × 0.586) ± (change in temperature of wall × hydrothermal equivalent of box) ± (change of temperature of body × hydrothermal equivalent of body) = total calories produced.

Th, thermocouple; Cu, inner copper wall; Cu<sub>2</sub>, outer copper wall; E, F, dead air spaces.

thermometers inside the box fail to make compensatory record, and the oxygen determination will be too low in that hour and too high in the next.

Analysis of the air in the interior of the chamber is made just before the beginning of each hour by passing ten liters of air from the box through three U-tubes containing, respectively, sulphuric acid, soda lime and sulphuric acid, then through a Bohr gas meter and back into the box again. This is called the "residual analysis."

Under the conditions present in the respiration apparatus, carbon dioxid is measured with the greatest ease and accuracy. Oxygen is also measured with accuracy if the person within the box lies perfectly quietly for ten minutes before the end of the period, whereas water production is the least accurate of all the determinations, on account of the varying hygroscopic condition of the walls, bedding and other surfaces within the closed spaces of the apparatus.

*The Measurement of Heat Produced.*—Roughly speaking, one-quarter of the heat eliminated by a man is present in the water vapor which is absorbed by the first sulphuric acid bottle on the absorber table. At 20 degrees C. 0.586 calories are contained as latent heat in 1 gm. of vaporized water.

The rest of the heat loss takes place by radiation and conduction. It is this heat which is measured by the calorimeter, itself. The mechanism of the calorimeter is essentially two-fold. In the first place, there is no heat loss through the walls of the apparatus, and, secondly, the heat produced by a man within is removed from the chamber by a current of cold water flowing through copper tubes suspended from the upper wall of the chamber. If the walls allowed no heat to pass, it is obvious that without the cooling effect of the water-pipes the temperature of the air in the box would soon attain the temperature of the human body instead of being about 23 C., at which it is usually held. The apparatus is therefore a constant-temperature, water-cooled calorimeter. It is evident that if no heat is allowed to pass through the walls of the calorimeter, then the heat produced within the chamber will be removed in the current of cold water flowing through the heat-absorbing pipes inside the chamber of the apparatus. If the temperatures of the ingoing and of the outgoing water are known and the quantity of water which has passed through the heat-absorber during an hour is measured, the quantity of heat carried away in the current of water can be accurately determined. For example, if the difference between the temperature of the ingoing and outgoing water is 2.50 degrees, and 20 liters of water have passed through the heat absorber in one hour, then 50 calories of heat have been carried away from the apparatus during the period. If the temperature of the walls within the apparatus has undergone a change this value is subject to corrections, but otherwise the total heat elimination of the person is meas-

ured by the 50 calories so determined plus the heat value of water vaporized during the hour.

To obtain an even flow of water through the heat-absorber the water is supplied from a constant-level tank placed above the calorimeter. To obtain ingoing water of an even temperature, Williams passed the previously ice-cooled water current through a Gouy temperature regulator and then through a current regulator designed by himself. These improvements allow the ingoing water to enter the calorimeter at a temperature which may not vary more than 0.02 C. during hours of experimentation and, for the first time, permitted the exact measurement of small quantities of heat in this type of apparatus. The temperatures of the ingoing and outgoing water are taken every four minutes by electrical resistance thermometers and are read in connection with a galvanometer and Kohlrausch bridge on an observer's table. The quantity of the water-flow is determined by weighing; the water is diverted at the call of "time," so that the exact quantity for the hour is collected in a previously weighed receptacle.

Having learned how the heat produced within the apparatus is carried away, the problem of how to prevent loss of heat through the walls of the chamber remains to be discussed. This was accomplished through a device introduced by Rosa. The calorimeter is constructed of three walls, an inner copper wall which has already been described as the lining of the respiration chamber, an outer copper wall separated from the inner wall by a space of dead air, and an insulating wall (made of two layers of "compo-board," the space between them being filled with cork), which insulating wall is separated from the outer copper wall by a second space containing dead air. It is obvious that if the inner and outer copper walls of the calorimeter have the same temperature there will be no exchange of heat between them. Therefore, to prevent a gain or loss of heat by the inner wall, it is necessary to maintain the outer wall always at exactly the same temperature as the inner wall, under which circumstances the latter cannot gain or lose heat to its neighbor.

In order to detect differences in temperature between the outer and inner walls Rosa arranged thermo-couples in series between the two walls. In this fashion the top, sides and bottom of the box are successively tested every four minutes by an operator at the observer's table to determine whether there is any difference in temperature between the outer and inner walls. If the outer wall is found to have a different temperature from the inner wall, its temperature is brought to that of the inner wall by the following device. A cooling current of water runs through pipes between the insulating and outer copper wall, and in this same space, along the line of the pipes, run "Therlo" resistance



wires carrying an electric current for the warming of this interspace (Fig. 1). By varying the intensity of the electric currents which severally supply the spaces to top, sides and bottom, the temperature of these spaces can be so controlled as to heat or cool the outer copper wall and maintain it at exactly the same temperature as the inner copper wall. This is the effective system which prevents a loss or gain of heat through the wall of the calorimeter.

Resistance thermometers are attached to the inner walls of the calorimeter, and if the temperature of the walls rises or falls between the beginning and end of the experiment, a correction must be made. It has been found that 19 calories are absorbed by the Sage calorimeter when the inner wall rises 1 degree. Conversely, 19 calories are given up by a fall of 1 degree. This is the *hydrothermal equivalent* of the box.

SCHEME OF EMPLOYMENT OF OBSERVERS IN A CALORIMETER EXPERIMENT

Period of Observation	Observer 1, at Electrical Control Table	Observer 2, in Charge of Experiment	Observer 3, Calculator
Eight minutes before	Brings wall into exact thermal equilibrium	Signals subject to lie absolutely quiet.	Starts passing first 10 L. sample of residual air through U tubes.
Five minutes before	.....	Starts kymograph record of movements of spirometer	.....
Four minutes before	.....	.....	Finishes first and starts second residual
One-half minute before	Takes final reading of air, wall and rectal temperature	Sets barometer	Finishes second residual
At "Time"	Presses button which diverts stream of water from weighing tank	Shuts spirometer off from box. Fills to standard level from oxygen tank.	Stops ventilating current of air. Turns valve to pass air through newly weighed absorbers. Starts ventilating current.
Immediately after "Time"	Starts taking readings every four minutes of ingoing and outgoing water, of air, walls, rectal and surface thermometers. Reads and adjusts temperature of top, sides and bottom of calorimeter, of the ingoing air and water every four minutes, or oftener if necessary.	Records and sets work-adder. Signals to subject that he may move. Weighs oxygen tank and connects with box again. Weighs sulphuric and soda lime bottles. Connects them up again and tests for leaks. During remainder of hour counts pulse, inspects valves for leaks, adjusts temperature of room, watches subject, etc	Weights water tank which has received all the water from the heat absorber during the past hour. Diverts stream of water to this tank again. Records barometer. Weighs residual. Calculates results of the hour just finished.

The temperature of the air entering the box from the absorbing table is always heated to exactly the same temperature as the air leaving the box.

Finally, an electric resistance thermometer inserted 10 or 12 cm. into the rectum of the person in the calorimeter gives information regarding the retention or loss of heat in his organism. The specific heat of a man is assumed to be 0.83, that is to say, 0.83 calory raises 1 kilogram 1 degree. If, therefore, the body temperature of a man weighing 70 kg. rises or falls 1 degree, the quantity of heat lost or

gained by the body will be  $70 \times 0.83$  or 58.1 calories. This is on the assumption that the rise of body temperature is everywhere the same as takes place in the rectum, a supposition which, unfortunately, is not always true.

The accompanying scheme (Table 1) gives the details regarding the employment of the three individuals who conduct a calorimeter experiment.

It may be added that special care has been taken to make the appearance of the calorimeter attractive to the eye, and that the spirit of the small ward in connection with the calorimeter work has been such that the patients have considered themselves especially fortunate when chosen for the diversion offered by a morning's occupancy of the apparatus.

#### CONCLUSION

The story of the Atwater-Rosa-Benedict calorimeter has been told here for the first time in brief, comprehensive, perhaps one might say semipopular language. The Williams calorimeter has shown the influence of many simple foodstuffs which were given to dogs in health and in induced disease. The Sage calorimeter reports "of the disturbances that Nature works and of her cures," without having, as concerns the sick human being, at any time, in the slightest degree, affected any patient to his disadvantage, but rather having yielded information regarding his condition which has been beneficial in his subsequent treatment.

It seems appropriate to recall the words with which Pettenkofer and Voit closed their communication regarding diabetes in the year 1867:

Even as anatomy has been separated from physiology, so from pathological anatomy pathological physiology will arise. Only thus will we be able to obtain a more exact knowledge of the character of disease than we now possess. Able pathologists have constantly sought to open up this field. It will gratify us if this work of ours which for the first time presents a complete picture of metabolism in disease shall inspire others to devote their abilities in this direction.

# CLINICAL CALORIMETRY

## SECOND PAPER

### THE RESPIRATION CALORIMETER OF THE RUSSELL SAGE INSTITUTE OF PATHOLOGY IN BELLEVUE HOSPITAL\*

J. A. RICHE AND G. F. SODERSTROM  
NEW YORK

#### CONTENTS

1. Previous descriptions of calorimeters.
2. The calorimeter room.
3. The wooden frame.
4. The copper walls and the insulating wall.
5. The absorber table, spirometer and heat absorbing system.
6. Rheostat board and observer's table.
7. Electric thermometers.
8. Telephone, fan and bed.
9. Electric and alcohol control experiments.
10. Limits of error in measuring heat, carbon dioxide and oxygen.
11. Determination of water elimination.
12. Adaptability of calorimeter to varying conditions.
13. Summary and conclusions.

During the short time in which the Sage calorimeter has been in operation there have been several requests for the technical details of the construction of the apparatus. It has therefore seemed advisable to publish a brief article for those interested in calorimeters. A complete description of the Atwater-Rosa-Benedict type of apparatus will be found in the monograph by Benedict and Carpenter.<sup>1</sup> A number of valuable improvements are added in the shorter article by Williams.<sup>2</sup> The earlier publications of Atwater and Rosa<sup>3</sup> and Atwater and Benedict<sup>4</sup> describe an apparatus fundamentally the same as that now employed, but for a complete understanding of the modern calorimeter it is necessary to consult the works of Benedict and Carpenter and

\* Submitted for publication Oct. 20, 1914.

\* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division of Bellevue Hospital.

1. Benedict and Carpenter: *Respiration Calorimeters for Studying the Respiratory Exchange and Energy Transformations of Man*, Carnegie Institution of Washington, 1910, Pub. 123.

2. Williams, H. B.: *Animal Calorimetry*, First Paper, A Small Respiratory Calorimeter, *Jour. Biol. Chem.*, 1912, vol. 31, 7.

3. Atwater and Rosa: *Description of a New Respiration Calorimeter*, U. S. Dept. Agriculture, 1899, Bull. 63.

4. Atwater and Benedict: *A Respiration Calorimeter with Appliances for the Direct Determination of Oxygen*, Carnegie Institution of Washington, 1905, Pub. 42.

Williams. The description by Langworthy and Milner<sup>5</sup> of their ingenious automatic calorimeter should also be consulted.

The Sage calorimeter resembles Benedict's bed calorimeter, but differs in a few details. On the recommendation of Dr. Langworthy and Mr. Milner of the Department of Agriculture the outside insulation was made of pressed cork and "Compo Board." The electrical resistance thermometers for the ingoing and outgoing water were also adopted on their advice. The gas wash bottles, water heating resistance and current regulator, water coil and several other improvements were copies of those used by Williams. The soda-lime bottles and spirometer resembled those described by Benedict<sup>6</sup> in connection with his small apparatus.

#### THE CALORIMETER ROOM

The small metabolism ward to be described is situated at the southwest corner of the new medical pavilion of Bellevue Hospital. To the north of this is a hall, now converted into a diet kitchen, which leads into the calorimeter room, formerly a small ward for convalescents. The room itself (Fig. 3) is about 5 meters square and 5 meters high. On the west side, opening on a covered balcony, is a large window in front of which stand a thermostat-controlled radiator and a "Simplex" electric heater. These are enclosed in a window box in such a manner, that by means of a blower, fresh air can be drawn in through the window, driven over the heaters and out into the room. Unfortunately, the daylight is not strong and needs to be supplemented by two powerful tungsten lamps.

In the center of the room stands the calorimeter, at the side of which is the observer's platform, raised a short distance above the floor to permit the passage of the numerous water pipes and electrical conduits. On the east side of the room is the panel box where the heavy feed wires are led up from the basement. Next to this panel box are the storage batteries with charging board used in electric checks. On the south side of the room, where the door is situated, enough space has been left to wheel a stretcher with a patient to the front of the calorimeter. By making careful use of every inch a great deal of apparatus has been placed in a small room without crowding those who work there.

#### THE FRAME

As the photographs show, the calorimeter was made high enough at the head to allow the subject to sit upright. This increases the

5. Langworthy and Milner: Year Book U. S. Dept. Agriculture, 1910, p. 307; *ibid.*, 1911, p. 491.

6. Benedict, F. G.: Ein Universalrespirationsapparat, *Deutsch. Arch. f. klin. Med.*, 1912, cvii, 156.



volume of contained air and magnifies certain errors, but makes the box much more comfortable and apparently gives better results than if the quarters were cramped. The frame (Fig. 4) was made of wood, as previous experience with the small calorimeter in Cornell had shown that the mass of angle iron between the metal walls made the box very sluggish in responding to temperature changes. To prevent warping, which would be disastrous, the best quality white pattern pine was used and the frame allowed to stand for several months before it was shellacked. The outside timbers were 6.35 by 6.35 cm. square and the braces 6.35 by 1.9 cm. All joints were glued and dowelled. The braces were spaced 30.48 cm. apart to give rigidity to the copper walls which are attached to the wood in many places.

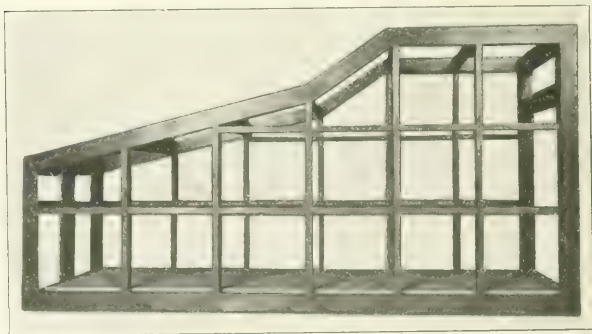


Fig. 4.—Wooden frame of calorimeter with asbestos board as floor.

#### COPPER WALLS

The inner copper wall (Fig. 5) forms an air-tight box 198.18 cm. long, 76.2 cm. wide, 91.4 cm. high at one end and 45.7 cm. at the other, with a capacity of 1,123 liters. At the head is an opening to serve as a door and on one side an opening for a window.

The wall is made of "16-ounce" sheet copper, tinned on the inside. It is fastened to the inner side of the wooden frame by means of brass angles soldered to the copper and screwed to the wood. The bottom rests on a long slab of asbestos board 9.5 mm. thick.

The outer copper wall (Fig. 6) which is screwed directly on the outer side of the wooden frame, does not come in metallic contact with the inner wall at any place except the rim around the large opening at the head of the box. This outer wall is made of "14-ounce" copper tinned on the outside, and while the joints are soldered they are not necessarily air-tight.



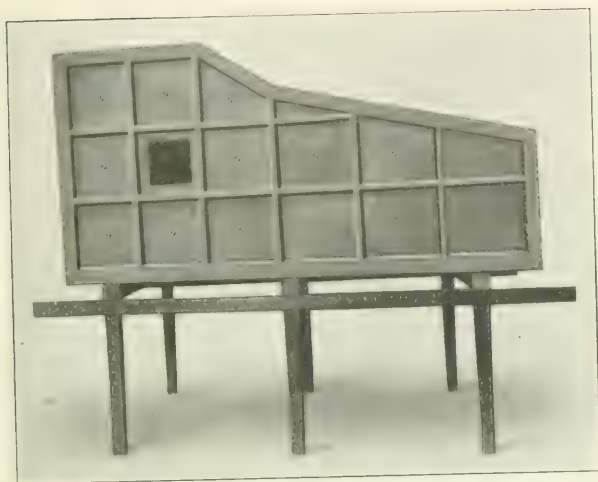


Fig. 5.—Inner copper box with brass thimbles for thermopiles.

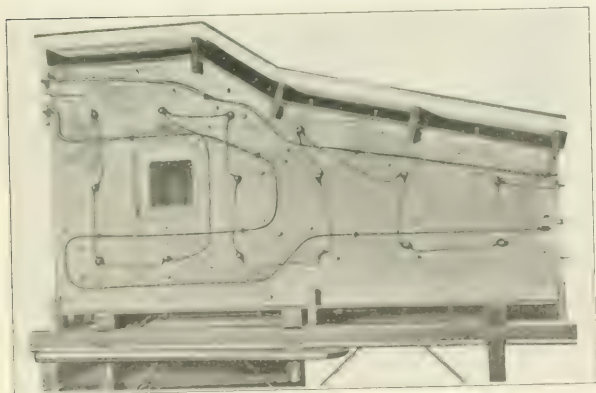


Fig. 6.—Outer copper box with leads connecting thermopiles, pipes for cold water and porcelain insulators for resistance wires. The wires themselves are not shown in the photograph. The top and bottom of the wooden box are in position.

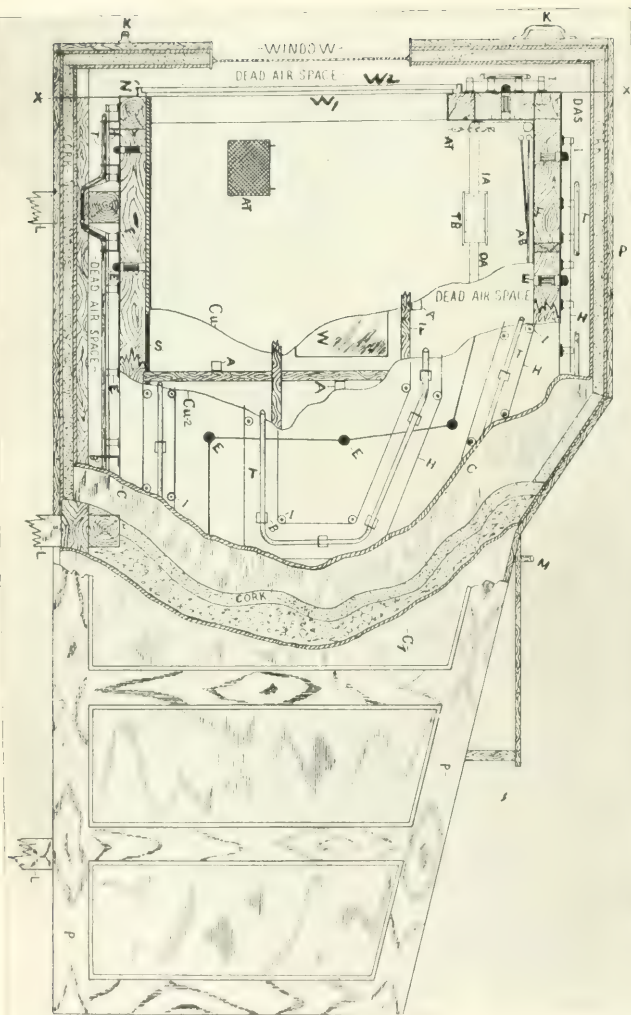


Fig. 7.—Sectional view of the calorimeter. A.A. Brass angles fastening inner copper wall to wooden frame. AT, Air thermometer. AB, Heat absorber pipes. BB, Brass angles supporting cold water pipes on the outer copper wall. C, Inner layer of "Compo Board." C<sub>1</sub>, Outer layer "Compo Board." Cu, Inner copper wall. Cu<sub>2</sub>, Outer copper wall. D.A.S., Dead air space. E.E., Thermopiles. F, Wooden frame. G, Resistance wire. H, Porcelain insulators. IA, Incoming air pipe. K, Handles of wooden panel at head of box removed at line X-X. L, Wooden legs of calorimeter. M, Pipe leading from interior of box to spirometer. N, Copper frame in which are placed glass plates W<sub>1</sub> and W<sub>2</sub>. O.A., Outgoing air pipe. P, Wooden supports for "Compo Board." S, Asbestos board under floor of calorimeter. TT, Cold water pipe. W, small window.

The braces of the wooden frame divide the dead air space between the walls into compartments about 30.48 cm. square and 6.35 cm. thick. In the center of each compartment is placed a thermopile with four thermocouples in thermal but not in electrical contact with each copper wall. The inner end of this thermopile fits in a brass thimble 25.4 mm. deep soldered to the outer side of the inner wall. The outer end (with its four thermocouples) fits in a brass tube which passes through the outer wall and is closed off from the outside air by P. B. Compound and electric tape.

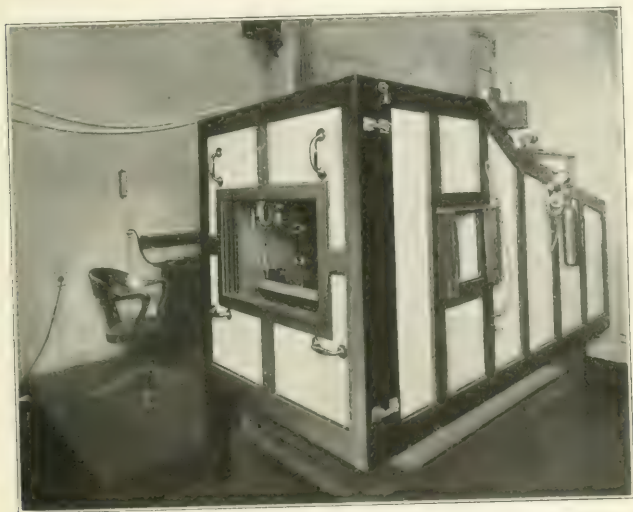


Fig. 8.—Calorimeter with front closed

In Figure 13 the large opening at the head of the box, measuring 76 by 70 cm., is closed by two glass plates 7.5 mm. thick, each sealed after the subject has entered the calorimeter by means of a mixture of 5 parts bees-wax and  $1\frac{1}{2}$  parts Venice turpentine. The small window in Figure 6 is permanently closed by glass plates fastened to the copper walls. There are numerous pipes and electric cables entering the box as will be described later.

On the surface of the outer copper wall are attached the wires connecting the thermopiles. The pipes for cold water are swung on brass angles attached to this surface and the enameled "Therlo" resistance wire is bound on insulators to the same surface, very much as described by Benedict and Carpenter.

## INSULATING WALL

Completely surrounding the outer copper wall and separated from it by a space of 7 cm. is the thick wall intended to protect the calorimeter from fluctuations in the room temperature. This is constructed of a layer of pressed cork 2.54 cm. thick, between two layers of "Compo Board," a patented building material made of strips of wood glued between layers of stout paper. This is supported by a framework of white-wood, making panels which are light, yet very effective as heat insulators. The head of the wooden box is provided with a glass window and furnished with handles so that it can be easily removed when the experiment is over and placed on a small shelf on the right of the calorimeter. The frame of this outer box is stained to resemble oak, and the "Compo Board" panels are painted with white enamel. Every effort has been made to make the room and the calorimeter pleasing to the eye, with the result that patients are attracted by the beauty of the apparatus rather than by its resemblance to a coffin.

## THE ABSORBER TABLE

The absorber table is so arranged that the air current is switched from one set of absorbers to the other by means of a three-way valve. This works satisfactorily and is much quicker than the old style seat-valves. The sulphuric bottles are larger models of the form described by Williams and hold about  $1\frac{1}{4}$  liters of acid, which will remove every trace of moisture until more than 100 grams has been absorbed. The soda-lime bottles resemble those devised by Benedict,<sup>9</sup> except for a modification of the tube which carries the entering air. This is divided in such a manner that the soda-lime can be packed about a brass pipe, the lower end of which is perforated and the upper end of which reaches almost to the top of the bottle, where it fits snugly in an elbow attached to the stopper. The Crowell blower is the same as the ones used by Williams and Benedict, but a safety device has been attached to prevent accidental reversal of the blower which would have disastrous effects. The two small bicarbonate cans next to the last sulphuric bottle did not remove entirely the acid vapors and it was necessary to place a long cylinder in the vertical pipe which carries the air from the absorber table. This contains about 340 grams of bicarbonate of soda packed between layers of cotton and catches all traces of acid fumes.

The air enters the box in a pipe which ends in a single opening directed just above the subject's head and leaves through a number of small openings in a pipe which runs across the foot of the box. A small electric fan at the lower end of the calorimeter keeps the air well stirred.

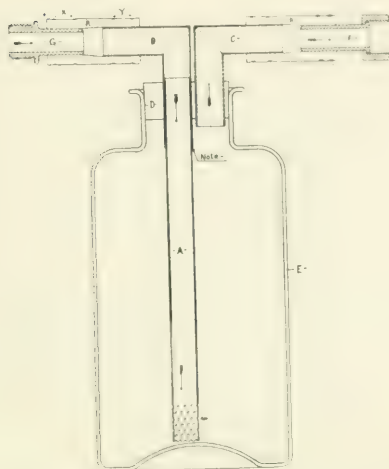
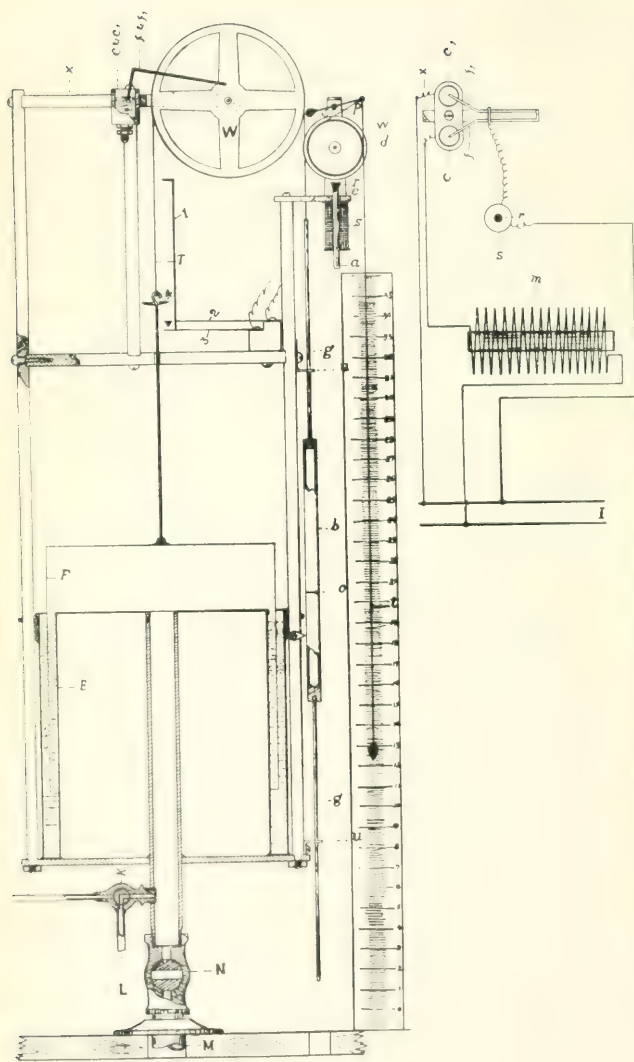


Fig. 9—Modified soda-lime bottle. A, Brass tube with perforated bottom and top which fits in brass elbow, B. The bottle is filled with A in position and the rubber stopper D with elbows B and C is then forced into neck of bottle. G and F, Brass couplings. R and R<sub>1</sub>, heavy rubber tubing. X and Y, Binding wires.



Fig. 10.—Safety device to prevent blower from being reversed. P, Pulley for belt to motor. S, Shaft of blower. H, Hub of wheel. K, Key 1, 2, 3, 4, 5, hardened steel rollers which engage when pulley is running in right direction, but disengage when pulley starts in opposite direction.



**Fig. 11.—Spirometer and Work-Adder.** M, Pipe from calorimeter to spirometer. N, two-way valve. J, Small pipe to ingoing air pipe. L, Oxygen inlet. K, Three-way valve arranged to admit oxygen into ingoing air pipe or into spirometer. T, String supporting bell. W, Wheel supporting bell. P, Spirometer bell of light copper. U, Spirometer tank filled with water. F, Spirometer bell of light copper. G, Guiding rod fitted loosely in uu. O, Mark on counterpoise. The spirometer bell, b, Counterpoise filled with mercury. IGG, Guiding rod fitted loosely in uu. O, Mark on counterpoise. The spirometer bell, c, is tilted at the end of each period until it is full. Small lever with eye through which thread passes. When the thread is pulled downward the cam is lifted. S, Solenoid. r, e, a, Plunger which is raised by solenoid, pressing against edge of work-adder while the spirometer bell is being raised by the admission of oxygen. f, Soft rubber; e, hard rubber, which raise plunger and port. c and ca, mercury cups into which dip f and g, when the spirometer bell sinks, making contacts which trigger plunger and energize magnet m, thus admitting oxygen. I, Low voltage current corresponding to I of Fig. 15. 1, 2, 3, 4, Automatic alarm



The spirometer on the top of the calorimeter resembles Benedict's<sup>6</sup> except that it is provided with a work-adder to record movement of the patient and not the total ventilation of the lungs. The bell is made of very light copper, is suspended in water and is carefully counterpoised. The counterpoise is provided with a writing point which records on a smoked paper the movements of the drum. To the wheel at the top is attached a brass arm with two points which dip into mercury cups set at slightly different levels whenever the spirometer bell

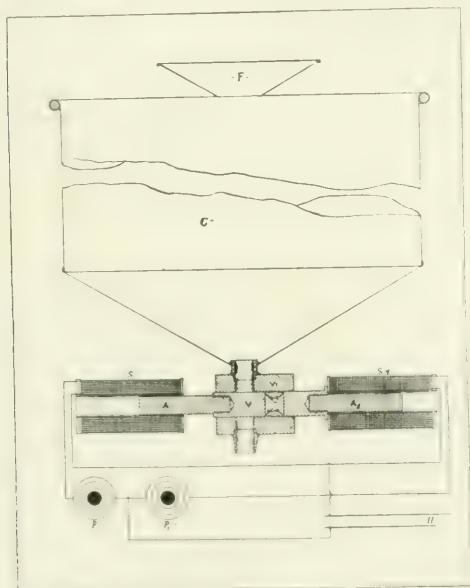


Fig. 12.—Electrical device for shutting and opening valve P. P. Push buttons controlling solenoids S and S<sub>1</sub>. A and A<sub>1</sub> iron cores attached to brass rod V. Valve is shown closed. When current is passed through S the Rod V will be drawn to the left and the narrow portion seen just under V<sub>1</sub> will come opposite the pipe leading from receiving can G.

sinks below a certain mark. One of these cups operates a magnet which opens the attachment that automatically admits the oxygen. This keeps the spirometer within about one centimeter of the same level unless the subject moves and suddenly heats the air locally. It is remarkable how promptly the spirometer rises when the person within the box makes even a slight movement of a hand or leg. In fact, it makes so delicate a

movement recorder that a Porter work-adder has been attached in such a manner that the downward movement of the counterpoise winds up a thread and the total amount of thread so wound represents the total work done by the patient during that particular period. By standardizing various movements of the body such as turning over or lifting the arm it is possible to gain a fairly accurate idea of the amount of mus-



Fig. 13.—View of open calorimeter. Patient on canvas bed partly in the chamber. On the left can be seen the observer's table and the rheostat board with the galvanometer. The rubber pipes for outgoing and ingoing air lead to the absorber table, a corner of which can be seen on the extreme left. In the background on the right are the storage batteries and charging panel.

cular movement and express it in centimeters of thread, thus obviating the necessity of printing long graphic records. In order to prevent the work-adder from winding up thread while the oxygen is being admitted,

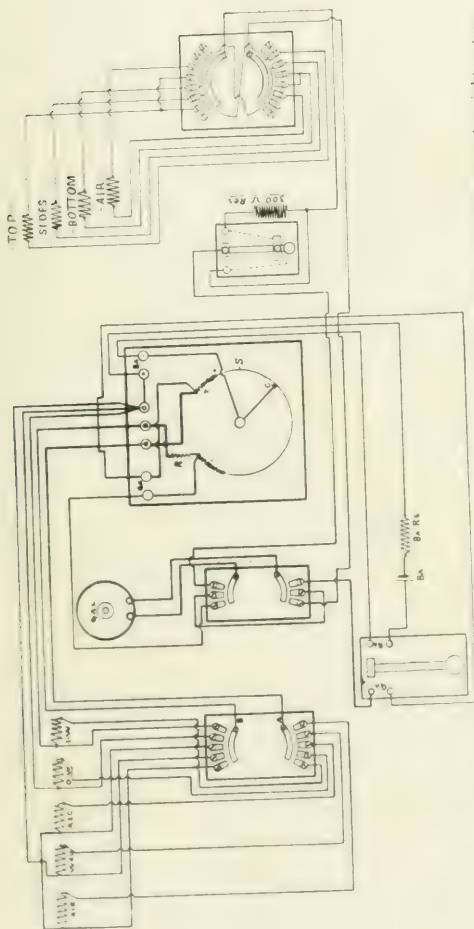


Fig. 14. Wiring diagram of observer's table. In the center is the Kohlrausch bridge, to the right a tapping key, with an arrangement for throwing in 300 ohms resistance when needed. This key is used in reading the thermopiles connected with the switch on the right. To the left of the bridge is a switch for connecting either thermopiles or resistance thermometers with the galvanometer. On the extreme left is the switch for the air, well, rectal, inguinal and outgoing water thermometers, each of which contains 100 ohms. Since this diagram was made two additional thermometers for surface temperature have been added. In the front of the table is a tapping key.

a solenoid is connected with the second mercury cup into which the brass arm on the wheel dips. This solenoid operates a small plunger which holds the work-adder while the magnet opens the oxygen valve and also maintains its hold for the instant after the oxygen has been shut off, since the spirometer rises somewhat slowly after the admission of oxygen. This solenoid lag, which corresponds to the spirometer lag, is secured by having the second mercury cup filled slightly more than the cup which controls the oxygen magnet.

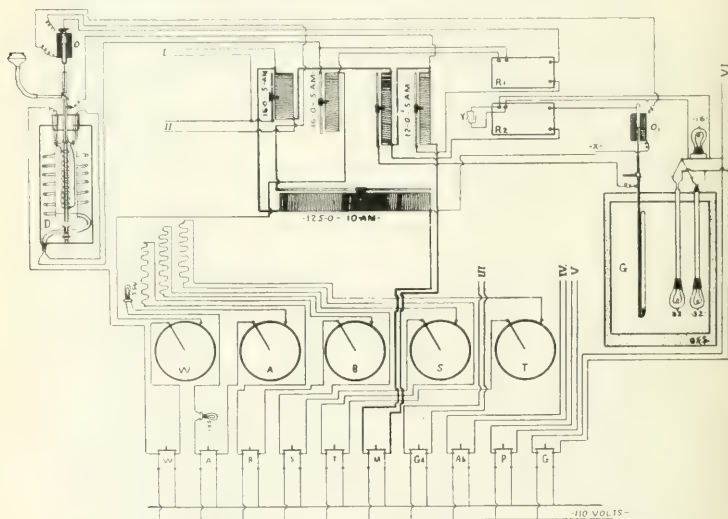


Fig. 15.—Wiring diagram of rheostat board. W, Switch and rheostat to control temperature of ingoing water in water heating resistance, D. A. Ingoing air. B, Bottom of calorimeter. S, Sides. T, Top. Ga, Galvanometer lamp. Ab, Motor on absorber table. P, Motor for pump. G, Lamps in Gouy regulator. M, Miscellaneous parts connected with tube rheostats. O, O1, Solenoid agitators lifting and dropping platinum contacts with mercury in Gouy and current regulator as the contact is made and broken mechanically at x. R1, Relay for current regulator. R2, Relay to control heating of lamps in Gouy.

The heat-absorbing system is the same as that described by Williams, the Gouy regulator and Williams' water heating resistance and current regulator giving very satisfactory results. The water coil suspended from the roof of the calorimeter has, however, been wound with brass "jack chain" to increase its absorbing surface. From this coil the water runs to the weighing tank on the platform of a "silk scale"

which is sensitive within 10 grams. The flow of water was formerly cut off by hand at the end of each period, but this is now done by a pair of solenoids controlled by the operator at the observer's table, thus reducing the staff by one man. The stream of water runs constantly through a can which has the capacity of 10 liters, and is provided at its lowest point with a valve that is opened and shut by the pair of solenoids above mentioned. At the end of a period the valve is shut and the water collects in the can while the tank is being weighed. After the weighing is finished the valve is opened and the water runs once more into the tank.

#### RHEOSTAT BOARD AND OBSERVER'S TABLE

The marble rheostat board and the observer's table resemble closely those described by Williams. This rheostat board, the panel box, charging panel for the storage batteries, conduits, wires, etc., were installed by the Electric Construction Supply Company after specifications kindly drawn up for us by the Department of Water Supply, Gas and Electricity of New York City. Directly above the rheostat board is mounted a galvanometer of the d'Arsonval type, provided with prisms so that the ascending ray of light from the lamp below is reflected from the mirror of the galvanometer downward to a scale just above the table. (Siemens and Halske.) This vertical mounting with scale that can be read by daylight saves a great deal of room. The galvanometer is braced securely and does not vibrate. To protect it from the dust it is covered with a thin copper hood. The resistance of the moving system is 45 ohms and there is a ballast resistance of 200 ohms in series, which, however, is not used.

Most of the precision switches used were furnished by Siemens and Halske, Catalogue Number 17327. One of similar design was made in our own shop. A new device which has given great satisfaction has been introduced into the switch connecting thermopiles with galvanometer. At the start of the experiment, or at any other time when the temperature differences between outer and inner walls are large, a resistance of 300 ohms is kept in series. As soon as the calorimeter is in balance a button on the switch is turned and the resistance short-circuited, making the adiabatic control extremely delicate. The Kohlrausch bridge provided by the Leeds and Northrup Company of Philadelphia is similar to the one described by Williams. The 60-step rheostat for controlling the temperature of the ingoing water and the four 45-step rheostats controlling that of the ingoing air, bottom, sides and top of the outer copper wall, were made by the Simplex Heater Company of Cambridge, Mass. They are mounted on the back of the board with their handles projecting through the board to the observer's

table. Just above them on the back of the marble slab are the five tube rheostats (Siemens and Halske) used to cut down the current to various small pieces of apparatus. On the front of the board are the two relays, one for the Williams water heating resistance and current regulator and the other for the Gouy regulator.

The thermopiles between outer and inner copper walls are arranged in three groups, thirty-two on the top, thirty on the sides and twelve on the bottom, the area covered by each group being warmed by a strand of enamelled "Therlo Wire," No. 24 B & S gauge, whose temperature is controlled by one of the step rheostats.

One thermopile is arranged with one end in the outgoing air current and the other in the ingoing air. The temperature of the latter is adjusted to that of the former by means of a step rheostat and two 55 volt lamps. A similar rheostat controls the temperature of the ingoing water by means of the water heating resistance.

#### THERMOMETERS

All thermometers contain 100 ohms resistance in nickel or platinum wire and are made on the three-lead system, being read on the same galvanometer used for the thermopiles. The water thermometers made by Leeds and Northrup are similar to those constructed by them for the automatic calorimeter of the Department of Agriculture. They are described in the Leeds and Northrup catalogue (Bulletin 811) and also by Dickinson and Mueller<sup>7</sup> of the United States Bureau of Standards. In our hands they have been most satisfactory, since they are more accurate, easier to calibrate, and easier to read than mercurials. The Leeds and Northrup air thermometer, similar to that used by Williams, is in eight divisions scattered over the inside of the box so as to give the average temperature of the air. They are connected in series by copper wire covered with rubber and a casing of lead, a combination made especially for us which has given good service. The wall thermometer consisting of eight divisions in series was made in this laboratory. Each division was made of No. 38 double silk covered nickel wire wound around a strip of mica and held 2 or 3 mm. from the inside of the inner copper wall. Over this was soldered a shallow copper box so that the resistance wire would lie in a small air space completely surrounded by metal at the temperature of the wall.

The rectal thermometer is of a new design made to respond more rapidly to changes in the temperature than the old type in which the resistance wire was surrounded by a jacket of dead air. The nickel wire with its double silk covering is wound on a small piece of ivory

7. Dickinson and Mueller: New Calorimetric Resistance Thermometers, Bull. Bureau Standards, 1913, ix, 483.



and dipped in a round ended silver tube filled with molten Wood's fusible alloy at a temperature of 96 C. This is solidified by dipping in water, thus forming direct metallic contact between the outside of the silver tube and the insulated wire. The leads from the thermometer are enclosed in a soft rubber tube. The surface thermometers are made of flat circular buttons of ivory 25 mm. in diameter and 5 mm. thick. One side of the button is hollowed out to a depth of 3 mm., the edges being filleted. On the bottom of this depression is wound concentrically the resistance wire. On this is poured the molten Wood's metal until it is flush with the original level of the ivory. Two of these units are used in series in each of the two surface thermometers. They are strapped to the skin with adhesive plaster and covered with a pad of cotton wool about 20 cm. in diameter and 4 cm. thick, this also being held in place with adhesive plaster.

The air thermometers were calibrated by the makers and the wall thermometers made to contain exactly the same resistance. Since they are used only to denote relative changes in temperature, a more exact calibration is not necessary. The rectal, surface and water thermometers are standardized several times a year by means of very accurate mercurials, certified by the *Physikalische Technische Reichsanstalt*. When calibrating them one notices that the electric thermometers all respond to temperature changes much more quickly than the mercurials.

The flexible rubber covered leads from the surface and rectal thermometers and the lead covered wires from the wall and air thermometers are carried to a ten-wire cable which perforates the calorimeter walls and is distributed on a hard rubber plate attached to the calorimeter and thence carried to the switches on the observer's table. The high tension currents from the calorimeter pass to a small hard rubber plate inside the box, thence in a separate strand cable to a slate board outside the calorimeter, and thence to the rheostat board. This cable carries leads for the telephone, electric fan and for the resistance coil used in electric checks.

#### ACCESSORY APPARATUS

The telephone, which has been made as light as possible, is seldom used, since the muscular work involved in telephoning is enough to affect seriously the results in rest experiments. The small electric fan placed in a corner at the foot of the calorimeter stirs the air thoroughly and allows one to get a good sample by drawing off ten liters through the large Bohr meter attached to the outgoing air pipe. The fan is run by the Edison storage batteries, giving off approximately 4.5 calories an hour, the exact amount being determined once an hour by a voltmeter and ammeter.

On the right side of the subject is a small glass shelf for the weighed urine bottles which, after each voiding, are placed on a spring balance that can be read through the window. Two small brass tubes are led through the wall of the calorimeter just below the small window. One acts as an emergency vent to prevent a positive or negative pressure at the beginning or end of an experiment when the ventilation is stopped. To the other is attached the Bowles stethoscope, which is strapped over the apex of the heart so that an observer outside can count the pulse at frequent intervals.

The inside of the calorimeter is formed by the polished tinned copper, the roof being almost hidden by the longitudinal absorber pipes wound with brass "jack chain." The calorimeter is wide enough for a man to turn comfortably from side to side, high enough at the foot to allow him to cross his legs and high enough at the head to allow him to sit upright.

#### THE BED

The bed in its present form is the result of much experimentation. The frame is made of varnished oak raised at the head so that the top is 12.7 cm. from the floor of the calorimeter while it is raised only 8.2 cm. at the foot. This allows for the sag of the waterproof canvas laced in the frame and keeps the subject 2 to 3 cm. from the copper floor. At the head is a back-rest with a piece of water-proof canvas, which is usually supplemented by a soft pillow. The bed is mounted on a pair of skids so that it can be pushed from the stretcher into the box. The canvas has proved to be much more comfortable than the springs and blankets formerly employed and has the advantage of absorbing very little water vapor. The varnished wood absorbs some water, the necessary clothing of the patient a great deal more, while the polished walls absorb only a minimum.

#### ELECTRIC AND ALCOHOL CONTROL EXPERIMENTS

The calorimeter has been tested repeatedly by dissipating known amounts of heat in resistance coils and by burning known amounts of alcohol. The apparatus and procedure used correspond almost exactly with those described by Williams and are similar to those previously used by Atwater and Benedict and by Benedict, Riche and Emmes.<sup>8</sup> In calculating the latent heat of the evaporation of water we have adopted the figures of Smith<sup>9</sup> and have given the latent heat the value of 0.584 large calories per gram of water evaporated at 23 C., the usual experimental temperature.

8. Benedict, Riche and Emmes: Control Tests of a Respiration Calorimeter, *Am. Jour. Physiol.*, 1910, xxvi, 1.

9. Smith, A. W.: Heat of Evaporation of Water. *Physical Review*, 1907, xxv, 145.

Date and Per Cent Absorb by Weight	Hour	Heat				Oxygen			Carbon Dioxide			Water			B. Q. Theory, 0.867
		Alcohol Returned, Gm.	Theory, Cal.	Found, Cal.	Error, Per Cent.	Theory, Gm.	Found, Gm.	Error, Per Cent.	Theory, Gm.	Found, Gm.	Error, Per Cent.	Theory, Gm.	Found, Gm.	Error, Per Cent.	
1883	1	10.14	66.35	64.52	-2.6	19.63	19.11	-2.2	17.49	17.81	+0.5	11.76	12.02	+0.8	0.662
1885	2	10.08	65.86	65.86	±0.0	19.41	18.08	-6.9	17.79	18.18	+2.3	11.69	11.82	+1.1	0.715
1886	3	9.85	64.62	64.39	-0.0	19.05	19.17	+0.6	17.46	17.41	-0.1	11.47	11.56	+0.8	0.692
1887	4	9.43	61.61	60.19	-1.8	18.16	17.99	-0.8	16.65	16.48	-1.0	10.94	11.10	+1.4	0.656
Average			64.52	63.79	-1.1	19.04	18.69	-2.4	17.45	17.48	+0.2	11.47	11.85	+3.4	0.676
1888	1	8.42	54.60	56.06	+2.7	16.69	16.61	+3.2	14.75	14.73	-0.1	9.75	10.20	+5.5	0.644
1889	2	8.19	53.04	52.39	-0.8	15.65	15.43	-1.4	14.85	14.30	-4.4	9.48	10.01	+5.6	0.671
1890	3	8.14	52.79	51.86	-1.7	15.56	15.39	-1.1	14.25	14.37	+0.8	9.43	9.94	+5.5	0.680
Average			53.14	51.87	-1.6	15.37	15.23	-0.9	14.08	13.82	-1.8	9.31	9.55	+2.5	0.660
1891	1	12.24	78.83	76.50	-3.0	23.22	23.20	-0.1	21.29	21.34	+0.2	14.15	14.73	+4.1	0.699
1892	2	12.36	79.60	80.48	+1.1	23.45	24.82	+5.8	21.50	21.98	+2.3	14.29	14.83	+3.7	0.644
1893	3	11.86	76.37	73.78	-3.3	22.50	20.55	-8.6	20.63	19.98	-3.0	13.71	13.53	-1.4	0.707
Average			78.37	76.92	-1.7	22.66	22.86	+0.8	21.14	21.10	-0.2	14.05	11.36	+2.2	0.673
1894	1	9.89	59.57	59.89	+0.5	17.54	17.62	+0.5	16.07	15.65	-2.7	10.43	10.85	+4.0	0.646
1895	2	9.79	59.97	61.39	+2.2	17.67	16.78	-5.0	16.29	15.75	-2.8	10.51	10.71	+1.9	0.682
1896	3	8.39	55.45	56.23	+1.5	16.34	15.98	-2.2	14.98	15.67	+4.6	9.72	10.30	+6.0	0.686
1897	4	9.79	62.62	61.05	+2.3	18.45	18.24	-1.2	16.91	16.82	-0.5	10.97	11.32	+3.2	0.671
Average			59.39	60.35	+1.6	17.50	17.16	-1.9	16.04	15.82	-1.3	10.41	10.80	+3.8	0.671
1898	1	10.41	67.20	67.34	+0.2	19.80	19.41	-2.0	18.15	18.22	+0.4	11.77	12.02	+2.0	0.683
1899	2	11.02	71.14	69.43	-2.4	20.66	19.33	-6.7	19.21	18.14	-5.6	12.46	12.13	-2.6	0.685
1900	3	10.80	70.39	70.36	+0.1	20.71	19.83	-4.7	18.69	18.61	-0.4	12.32	12.62	+2.5	0.696
1904	4	10.94	64.81	66.29	+2.3	19.10	20.13	+5.4	17.50	17.75	+1.4	11.36	11.95	+5.2	0.641
Average			68.36	68.30	+0.0	20.14	19.60	-2.6	18.46	18.13	-1.5	11.98	12.18	+1.7	0.675
Total			1216.72	1212.61	-0.33	388.56	385.60	-1.69	338.67	328.45	-0.68	215.62	222.18	+3.09	Av. 0.672

\* All periods one hour long.

It has seemed advisable to publish all the electric and alcohol checks made with the calorimeter. In publishing control tests the results are much more striking if one selects only the best and leaves out those in which the agreement is not close. This method expresses only the minimum error while the things we really need to know are the average, maximum and total errors. The total error shows the accuracy of the method, the maximum error may occur in the course of any experiment, while the average error is with us always. The minimum error

TABLE 2.—ELECTRIC CHECKS

Date	Length of Period, Min.	Calories, Theory	Calories, Found	Per Cent. Error	Date	Length of Period, Min.	Calories, Theory	Calories, Found	Per Cent. Error
3/4/13	60	72.25	73.19	+1.2	11/28/13	60	78.22	77.15	-1.4
	60	72.25	72.19	+0.0		60	78.22	77.62	-0.8
Average	..	72.25	72.69	+0.6		60	78.22	78.67	+0.6
4/5/13	60	80.78	77.26	-4.4	Average	..	78.22	77.81	-0.5
	00	80.78	79.31	-1.8					
Average	..	80.78	78.29	-3.1	1/26/14	60	76.92	75.86	-1.4
10/13/13	30	41.74	42.15	+1.0		60	76.92	77.41	+0.6
	30	41.74	41.56	-0.4		60	76.92	77.88	+1.3
	30	41.74	41.25	-1.2		60	76.92	77.24	+0.4
	30	41.74	41.10	-1.5	Average	..	76.92	77.10	+0.2
	30	41.74	41.35	-0.8					
Average	..	41.74	41.49	-0.6	5/11/14	60A	78.71	80.03	*
10/22/13	60	83.98	83.98	±0.0		60B	78.22	75.18	....
	60	83.98	83.83	-0.2		30C	39.07	41.35	....
	60	83.98	84.02	+0.0	Total....	150	196.00	196.56	+0.3
	60	83.98	83.84	-0.2					
Average	..	83.98	83.92	-0.1	Total of all checks	..	1589.02	1583.42	-3.5

\* A, B, C. Temperature changes of wall of calorimeter: A, +0.06 C.; B, -0.73 C.; C, -0.05 C. Test to verify hydrothermal equivalent.

is a joy to behold, but it does not occur with the regularity inferred by the prominence it is usually given. If, for instance, we should publish only the electric check of October 22 with an hourly error of 0.2 per cent., and the alcohol check of April 30, in which the total errors in the measurement of heat, oxygen and carbon dioxid are all less than  $\frac{1}{2}$  of 1 per cent., we should give a false impression of accuracy. This test shows that the calorimeter is capable of measuring heat, oxygen and carbon dioxid with a maximum error of 1.8 per cent. in three consecutive hours. Even better results could be obtained if greater care were taken to secure an even combustion of alcohol. On the other

hand, the errors which can occur in hourly periods and in whole experiments are shown in Table 3. The average error has been obtained by multiplying each per cent. of error by the number of times it occurs and dividing the total by the number of periods. In the whole series of experiments of three or four hours' duration the average error for heat is 0.9 per cent., for oxygen 1.6 per cent. and for carbon dioxide 0.6 per cent., while for the individual hours the error is 1.2 per cent., 3.2 per cent. and 1.6 per cent., respectively. The total error in all the

TABLE 3.—SUMMARY OF ERRORS IN ELECTRIC AND ALCOHOL CHECKS

Per Cent. Error	Average of Whole Experiment				Individual Hours			
	Cal.	O <sub>2</sub>	CO <sub>2</sub>	H <sub>2</sub> O	Cal.	O <sub>2</sub>	CO <sub>2</sub>	H <sub>2</sub> O
0.....	5	1	3	..	10	1	5	..
1.....	4	1	1	..	15	7	5	4
2.....	2	2	1	2	9	3	5	2
3.....	1	1	..	1	4	1	3	4
4.....	..	..	..	1	1	..	..	5
5.....	..	..	..	1	..	2	..	1
6.....	..	..	..	..	..	2	1	4
7.....	..	..	..	..	..	1	..	..
8.....	..	..	..	..	..	1	..	..
9.....	..	..	..	..	..	1	..	..
10.....	..	..	..	..	..	..	..	1
Total number of experiments or hours.....	12	5	5	5	39	19	19	19
Average error...	0.9	1.6	0.6	3.2	1.2	3.2	1.6	3.7
Total error.....	-0.33	-1.69	-0.63	+3.09				

electric and alcohol checks is: heat, -0.32 per cent., O<sub>2</sub> -1.69 per cent., CO<sub>2</sub> -0.68 per cent. The total error in the water is +3.09 per cent.

The electric checks show a smaller error in the measurement of calories than the alcohol, since the dissipation of heat is much more uniform. It is difficult to secure an even flow of alcohol to the burner and the larger errors in the oxygen determination are due to irregularities in the flow during the last five minutes of the period. If a slight negative pressure develops within the box toward the end of the period, alcohol is sucked into the burner causing the flame to flare up

and expand the air before the air thermometers record the rise in temperature. This causes an error in the oxygen calculation which, as the tables show, is usually corrected the next hour. With a trained human subject the production of heat and carbon dioxide and the absorption of oxygen are more regular than in the case of an alcohol check and the error presumably not so large. The cause for the negative total error in the measurement of heat,  $O_2$  and  $CO_2$ , is not clear, but one cannot help suspecting that a slight absorption of water by the alcohol and a slight evaporation as the alcohol drops from the bottle into the buret may account for most of the error. In experiments on man there is another factor which reduces an error in the measurement of oxygen or carbon dioxide considerably. In calculating the indirect calorimetry the factor by which the oxygen or carbon dioxide is multiplied changes with the respiratory quotient and it happens that a plus error in measurement of the gas is partially offset by a minus change in the factor. This change reduces the error to an extent varying between one-fifth and three-quarters of its original size, unless the errors in both gases are in the same direction, leaving the quotient unaltered. The accuracy of the calorimeter has also been demonstrated by the close agreement of the methods of direct and indirect calorimetry. This will be taken up in detail in the paper on normal controls, but at this point it may be said that in a total measurement of 4,577 calories the two methods agreed within 0.17 per cent., and that in 26-hourly periods on the normal control most carefully studied, the agreement was within 5 per cent. in seventeen of the hours.

In spite of the fact that some of the errors published in the table are larger than those published in connection with other types of apparatus, we feel justified in believing that the Sage calorimeter is the most accurate and most reliable instrument of its size used in the study of the respiratory metabolism. The table includes all the alcohol and electric checks, good, bad and indifferent, made during the period when the machine was used for experiments. The only ones left out are those made at the beginning of the season while the apparatus was being put in order, and actual work was never begun before obtaining a check good enough to publish. To the best of our knowledge this method of publishing all the tests has never been used in connection with other types of respiration apparatus, and we have no detailed information as to their average, maximum and total errors.

It is to be regretted that we have not been able to make long electric tests to determine the hydrothermal equivalent of the calorimeter. The storage batteries are not powerful enough to furnish current for more than four hours in addition to the preliminary period of 30 to 40 minutes, and we have never felt justified in using the house current



with its variations in voltage. Numerous short tests showed that the hydrothermal equivalent was very close to 19 liters of water, and this figure gave results within 0.3 per cent. in the check of May 11 with a large temperature change in the second hour. Incidentally, the advantage of a wooden frame is shown by the rapidity with which the box responded to this temperature variation.

#### DETERMINATION OF WATER ELIMINATION

In all types of respiration apparatus the measurement of the water elimination has presented great difficulties. This was studied in detail by Benedict, Riche and Emmes, who found that long experimental periods were required to obtain accurate results. The interior of the Sage calorimeter is tinned and polished and there is very little wood-work and cloth, but still a considerable amount of moisture can be retained within the box. In alcohol checks with a water production of only 10 to 14 grams an hour the air becomes dryer and dryer, and this moisture is given off during the whole test, making uniformly a plus error. In experiments on normal men the water elimination is about twice this amount and the percentage of moisture changes but little from hour to hour. In patients who have a tendency to sweat, the water given off may amount to 35 to 40 grams an hour, and there is a tendency for the percentage in the air to increase steadily and finally reach the point of saturation. We should expect a plus error in the determination as the air becomes dryer, a minus error as the percentage of moisture increases, and no error while equilibrium is being maintained. After the first hour of an experiment on man it seems fair to expect an error of less than 5 per cent., except in extreme cases of sweating. More accurate results could be obtained only by removing all wood-work, stripping the man naked and increasing the ventilating current. This would involve such artificial conditions that the results would be worthless.

#### ADAPTABILITY OF CALORIMETER

By carefully controlling the rate of flow and the temperature of the water in the heat-absorber it is possible to adapt the calorimeter to wide variations in the heat production of the subjects. For example, on April 23, 1914, an experiment was made on a cretin with an average heat production of 26 calories an hour. The next day the subject was a patient with exophthalmic goiter, whose heat production averaged 107 calories. In one case the methods of direct and indirect calorimetry agreed within 0.2 per cent., and in the other within 0.7 per cent. It has also been possible to adapt the calorimeter rapidly to changes in the heat production from hour to hour by changing the temperature of the

ingoing water and in extreme cases by changing the rate of flow at the beginning of a period.

It has been possible in a long series of experiments for two men to take all the readings and make all the calculations in hourly periods. Three men can handle the apparatus with ease during the trying experiments, and most of the alcohol checks, which are much more difficult, have been made with only three in the room. As a rule, the staff arrives shortly before nine o'clock in the morning, makes a three-hour experiment, gets everything in readiness for the next day and leaves the calorimeter room about three or four o'clock in the afternoon. It has been possible, on occasions, to make six experiments in a week. The calorimeter has been very seldom out of commission. Between October 13, 1913, and May 18, 1914, it was possible to make 113 experiments on man and eight alcohol and electric checks.

#### SUMMARY AND CONCLUSIONS

The original Atwater-Rosa respiration calorimeter with the improvements added by Benedict, Williams and others has been adapted for clinical study in Bellevue Hospital. The form of the apparatus makes it perfectly comfortable for patients. The accuracy is such that in observations lasting three or four hours the heat production, carbon dioxid elimination and oxygen consumption as determined by alcohol and electric tests can be measured with an average error of 0.9 per cent., 0.6 per cent. and 1.6 per cent., respectively. In periods one hour long the average error for heat measurement was 1.2 per cent., for carbon dioxid 1.6 per cent. and for oxygen 3.2 per cent.

The calorimeter never needs more than three men for its operation, and two men have repeatedly made all the readings and all the calculations in hourly periods.

## CLINICAL CALORIMETRY

### THIRD PAPER

#### THE ORGANIZATION OF A SMALL METABOLISM WARD\*

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NEW YORK

All investigators who have attempted to carry on metabolism experiments in hospitals have experienced more or less difficulty in the administration of the diets and the collection of the excreta. The necessity for a special metabolism ward became evident as soon as it was decided to build a respiration calorimeter in Bellevue Hospital. Through the generosity of the trustees of the hospital and the attending staff of the Second Medical Division a small ward holding four or five beds was placed in charge of the medical director of the Russell Sage Institute of Pathology,<sup>1</sup> who was also one of the junior members of the attending staff of the hospital. He is directly responsible to the attending physician for the welfare of the patients, and there has always been a spirit of active cooperation between the small metabolism ward and the large medical wards of the service.

The calorimeter room described in the preceding paper<sup>2</sup> is located on the same floor as the male medical wards of the Second Division in the new Medical Pavilion. The side hall, used as an entrance to the calorimeter room, has been partitioned off to make a small diet kitchen. Next to this is a well lighted ward of four beds used almost exclusively for patients whose metabolism is the subject of active investigation.

The patients are cared for by three graduate nurses, trained in metabolism work and paid by the Institute. The success of the ward is in large measure due to the faithful and intelligent work of the head nurse, Miss Estelle Magill, and her two assistants. They have used the same care in the preparation of food and the collection of excreta that is used in the laboratory and the effort has constantly been made to keep the error within 1 per cent. In order to maintain a high degree of accuracy and at the same time a high standard of nursing it is necessary for the three nurses to devote their whole time to the ward of only four patients. Orderlies, the greatest source of error in metab-

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\* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital, New York.

1. Dr. Eugene F. DuBois.

2. Riche and Soderstrom: See p. 805.

olism work, are excluded from the ward and patients are never allowed in the hospital dining room or kitchen, and only the most trusted are permitted to leave the room at all. These precautions are necessary in order to afford the certainty that the twenty-four-hour specimens of urine are complete and that the patients have not smuggled in outside food. Patients are not allowed out of sight of the nurse in charge for more than a couple of minutes at a time.

The food supplied to patients in the metabolism ward is all prepared by the special nurses, who have become so skilled in the preparation of the various dishes that they can even make one-sided diets attractive. In fact, the patients enjoy the cooking so much that they are sent to their homes or to the general hospital ward with difficulty. This is a matter of importance when one desires to keep interesting cases under observation. The foods are prepared as often as possible from raw materials whose composition is determined from time to time. Milk and cream have been of fairly constant composition, as the analyses over a period of several years have shown.

By applying some of the principles of business efficiency, the work has been made a great deal easier. The dry cereals, eggs, bacon, etc., are weighed in white enamel dishes and bowls of known weight marked with serial numbers. Milk and cream are measured in measuring cylinders and added to these dishes in which the food is baked, fried or boiled. The dishes with the cooked food are then taken directly to the patient and if by any chance he should leave some of the food it is an easy matter to weigh it back. Egg whites and yolks are weighed separately. Sugars, salt, cocoa, butter, etc., are put up in packages of known weight by the night nurse to save time during the day.

When a patient first enters the ward the nurses spend a couple of days in investigating his dietetic limitations and his dislikes, a matter of great importance. A diet such as the following, for example, is then ordered: 3,000 calories, 15 grams nitrogen,  $\frac{1}{2}$  non-protein calories in fat,  $\frac{1}{2}$  in carbohydrate. The nurses then work out a diet which will fulfil the specifications and at the same time be agreeable to the patient. Often by careful work it is possible to educate a patient to a diet that he could not otherwise tolerate. We cannot too strongly emphasize the need of individualization aided by good cooking in experimental metabolism work.

The method of collecting twenty-four-hour specimens is, we believe, a new one, and since it has proved to be very satisfactory, should be given in detail. A large number of 20-ounce, round, wide-mouthed bottles with cork stoppers are kept in the ward. These have been etched on the side so that one can write on them with a pencil. At 5 a. m., the time at which the twenty-four-hour period ends, each

## COMPOSITION OF FOODS USED IN METABOLISM WARD

Food	Protein	Fat	Carbo- hydrate	Calories per Gram	100 Calory Portion
Beef, chopped .....	22.1-48.6	2.4-12.8	0	1.3- 2.0	50- 79
Beef broth .....	2.1	0.2	0	0.1	1000
Bread, white .....	9.8	0.3	53.5	2.6	38
Chicken, minced .....	18.5	7.2	0	1.5- 1.5	69
Cabbage, thrice boiled*....	.....	.....	0.24	.....	.....
Cauliflower, thrice boiled*	1.75	.....	0.12	.....	.....
Cocoa, powdered .....	23.1-23.2	19.4-25.2	48.3-54.0	4.8- 5.3	19- 21
Cheese, cottage .....	14.9-19.2	0.2- 1.9	0	0.6- 0.9	118-164
Crackers, soda .....	8.3	9.3	73.2	4.3	24
Crackers, sugar .....	6.2	10.7	80.1	4.5	22
Cream .....	2.1- 2.9	17.1-19.8	4.0-5.2	1.9-2.1	48- 53
Cream .....	2.1-2.9	17.1-19.8	4.0-5.2	1.9-2.1	48-53
Custard .....	5.4	3.5	21.6	1.4	70
Custard, hospital diabetic	5.7	5.7	7.3	1.1	94
Farina, dry .....	18.9	0.9	68.2	3.7	27
Flour, hospital diabetic....	23.2	1.3	68.2	3.9	26
Ice cream, vanilla.....	3.4- 4.8	1.7- 6.9	12.2-23.4	1.0- 1.6	61- 99
Ice cream, chocolate.....	3.7	5.5	12.3	1.2	85
Jelly, lemon .....	2.1	0.2	17.1	0.9	111
Junket .....	2.1	2.1	16.6	1.0	104
Macaroni, dry .....	13.7	1.2	77.5	3.9	26
Mammala .....	26.8	9.6	.....	4.2	24
Mammala (separated milk)	31.7	5.4	.....	4.0	26
Mammala (full cream)....	10.2	28.2	.....	5.5	18
Milk, hospital .....	3.09- 3.1	3.3- 4.67	4.10- 4.7	0.6	166
Oatmeal, dry .....	15.1	5.6	71.2	4.1	24
Potatoes, mashed .....	2.2	0.2	18.0	0.9	118
Pudding, rice .....	4.1	3.0	24.8	1.5	68
Pudding, tapioca .....	5.7	2.3	14.8	1.1	94
Rice, dry .....	7.0	0.5	81.9	3.8	27
Rice, cooked .....	1.4	0.3	13.1	0.6	159
Tapioca .....	.....	.....	91.1	3.7	27
Special Articles—					
Cane sugar .....	Sucrose 100 per cent. ....			3.66	25.2
Corn sirup—glucose.....	Glucose, 41.3 per cent.; dextrin, 33.9 per cent.; sucrose, 2.7 per cent.			3.07	32.6
Corn sirup—glucose.....	Glucose, 42.4 per cent.; dextrin, 44.6 per cent.; sucrose, 0.				
Gelatin .....	.....			37.0	27.0
Lactose .....	Lactose, 98.4 per cent. ....			9.52	10.5
Olive oil .....	.....			1.46	68.5c.c.
Sherry .....	Alcohol by volume, 19.45 per cent.; Carbohydrate, 1.96 per cent.				
Vinegar .....	Acetic acid, 4.07 per cent.			2.96	33.8c.c.
Whisky .....	Alcohol by volume, 41.76 per cent.				

\* Cooked in three changes of water.

patient is given a bottle and made to empty his bladder. The bottle is then marked with his name, the date, the hour and minute. The volume is estimated for clinical purposes by comparison with a calibrated bottle of the same capacity. The data are then recorded on a special slip of paper to go to the laboratory and also on the diet chart. A little toluene is added to the urine bottle, which is corked and stored in the ice-box along with the previous voidings of that twenty-four-hour period, each voiding being in a separate bottle. At about 9 o'clock in the morning the laboratory man checks up the bottles with the records on the laboratory slip, and with the nurse's notes takes all the bottles to the laboratory, measures the volume accurately, makes up to volume and analyzes a sample.

The only disadvantage of this system is the labor of carrying a number of half-filled bottles, although this is not great if suitable carriers are used. The advantages are as follows: 1. There is no chance of a specimen of urine having been poured into another patient's bottle thus spoiling two twenty-four-hour specimens. 2. If a single voiding is lost the urine for the remainder of the day can be accurately analyzed. 3. The urine can be fractionated and the nitrogen elimination determined in hourly periods, as is frequently done in calorimeter experiments. 4. The bottles make excellent urinals, are less apt to spill than the ordinary ward urinal and are not unsightly even when filled with urine. 5. Since the urines are made up to volume in the laboratory, it is possible to rinse out each bottle with distilled water and collect every drop of urine. 6. The bottles are washed, dried, and, if necessary, sterilized in the laboratory, so that there is no danger of a patient voiding into a urinal containing decomposing urine. 7. The bottles are cheap and can be kept on hand in large numbers, so that the patients need never wait for the urinal. 8. While we have never had occasion to use them in a general ward, there is no reason why they should not be used instead of the common type of expensive and unsightly urinal. In collecting single specimens for the usual routine analysis the nurse could put a bottle by each bed in the morning and send the desired specimens directly to the ward laboratory without transferring to a special jar. It is surprising how long urines will remain clear if voided into and kept in a clean bottle.

The collection of feces is somewhat more difficult. Patients who can get out of bed defecate into a weighed bucket in the commode. This bucket is then weighed again. A little formalin is added and the whole sent to the laboratory where the specimen is thoroughly mixed and one-tenth removed to be dried and added to the other aliquot portions of that period and analyzed. Bed-ridden patients use a weighed bed pan from which the feces are transferred to a covered bucket for



transportation. Most of the patients with acute diseases are given every morning an enema of hypertonic salt solution. Oil and soap enemas of course interfere with the accuracy of the fat analyses; glycerin enemas make it impossible to dry the feces. To divide the periods, powdered carmin (0.3 gm., 5 grains) is given with the first meal of the period and with the first meal after the period is ended. Experience has shown that it is much easier to determine the exact point of appearance of the carmin in the feces than to find the point of disappearance. When patients are being given enemas it is easier to discover traces of carmin than traces of charcoal. Periods are made as long as possible to minimize the errors of division.

A special diet sheet has been provided by the hospital on which the nurses record the weights of raw material given to the patient and make the calculations from the table of known composition of the food. On this sheet is a summary column giving carbohydrate, fat and protein grams and calories, total calories, nitrogen of the food, of the urine, of the total excreta and the nitrogen balance; weight of the patient and food calories per kilogram. In another place are columns for recording the time and amount of each voiding and each defecation.

Patients are weighed at 9.00 a. m. every day or every other day on a "silk scale" accurate to 10 grams. Bed patients are weighed on a platform resting on these scales in the manner described by Coleman.<sup>3</sup> The nurse slides the patient on the smooth platform which is just at the level of the bed, weighs him and then makes up the bed while he is still on the balance. The whole procedure has been found to be a convenience for the nurse rather than a time-consuming task.

Nitrogen determinations are made by the Kjeldahl method, ammonia, uric acid, creatin, creatinin, and indican by Folin's<sup>4</sup> methods, urea and glucose by the methods of Stanley R. Benedict.<sup>5</sup>

The calorific value of the foods has been determined by means of the Riche<sup>6</sup> bomb calorimeter. Food fat analyses have been made in a Soxhlet apparatus. Carbohydrates were determined by a difference using in the later work a new procedure described by Gephart.<sup>7</sup> The

3. Coleman: Diet in Typhoid Fever: *Journal Am. Med. Assn.*, 1909, liii, 1145.

4. Folin: Approximately Complete Analysis of Thirty Normal Urines, *Am. Jour. Physiol.*, 1905, xiii, 45.

5. Benedict: The Detection and Estimation of Glucose in Urine, *Jour. Am. Med. Assn.*, 1911, lvii, 1193. The Estimation of Urea in Urine, *Jour. Biol. Chem.*, 1910, viii, 405.

6. Riche: An Improved Type of Calorimeter for use with any Calorimetric Bomb, *Jour. Am. Chem. Soc.*, 1913, xxxv, 1747.

7. Gephart, Frank C., and Csonka: In the Estimation of Fat in Feces, *Jour. Biol. Chem.*, 1914, xix, 521.

dried feces were powdered and the fat determined at first by the Kumagawa-Suto method and later by the new saponification procedure described by Gephart.<sup>7</sup> In calculating food values, Rubner's factors were used, namely: for fat 9.3 calories; for carbohydrate and protein, 4.1 calories per gram.

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8. Kumagawa and Suto: Ein neues Verfahren zur quantitativen Bestimmungen des Fettes und der unverseifbaren Substanzen in tierschen Material nebst der Kritik einiger gebräuchlichen Material, *Biochem. Ztschr.*, 1908, viii, 212.

# CLINICAL CALORIMETRY

## FOURTH PAPER

### THE DETERMINATION OF THE BASAL METABOLISM OF NORMAL MEN AND THE EFFECT OF FOOD\*

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#### TABLE OF CONTENTS

1. Introduction.
2. Review of literature on basal metabolism.
3. Review of literature on specific dynamic action of foods.
4. Experimental procedure.
5. Description of subjects and details of experiments.
6. Tables of experimental data.
7. Discussion of results:
  - a. Comparison of direct and indirect calorimetry.
  - b. Comparison of surface and rectal temperature.
  - c. Selection of the average normal standard.
  - d. Variations from this standard found in normal individuals.
  - e. Calories per square meter versus calories per kilogram.
  - f. Increased metabolism following the ingestion of protein and carbohydrate.
8. Summary and conclusions.

The importance of the normal control has been emphasized so strongly by the serologists and the management of the control has been developed by them to such an art that it has seemed advisable to apply some of their methods of critique to the study of the respiratory metabolism. Serologists insist that a man shall make his own controls with the same apparatus and exactly the same technic as in the experiments and they also insist that the controls shall be numerous enough to show individual variations in their true proportions. These precautions and many others have been made necessary by the fact that the normal control is usually the point of attack in serological controversies. Likewise in the study of metabolism the normal control is coming to be recognized as the weakest part of the experiment. The chemical methods of blanks and duplicates will not suffice; the living organism is the uncertain factor. The literature is notoriously filled with false theories, of which by far the greater part would never have been promulgated if sufficient attention had been given to normal controls.

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‡ With the technical assistance of G. F. Soderstrom and R. H. Harries.

The three papers immediately preceding have described the Sage respiration calorimeter in Bellevue Hospital and its adjoining metabolism ward. Before presenting any of the work in pathological conditions it has seemed best to study in detail the results obtained on the normal controls. It was the original intention to use a large number of normal subjects and determine the individual variations in metabolism, but this laborious piece of work was gladly abandoned when it was learned that Benedict and his collaborators were engaged in the task. In pathological conditions the work has been confined as much as possible to men between the ages of 20 and 50 who do not depart very markedly from the normal relationship between height and weight. Consequently the normal controls have been selected to comply with these requirements.

#### BASAL METABOLISM

As a basis of comparisons between all normal individuals and groups of patients the heat production in the morning from fourteen to eighteen hours after the last meal with the individual at complete rest, was selected. This has been termed the "*nüchtern*" metabolism by the Germans, the "post-absorptive" by Benedict and Cathcart,<sup>1</sup> but the simplest and most satisfactory term is "basal metabolism," a translation of the German *Grundumsatz*, as used by Lusk and his coworkers<sup>2</sup> in the series of papers published under the heading of Animal Calorimetry.

The literature of the respiratory metabolism of healthy men has been admirably reviewed by Benedict and Carpenter<sup>3</sup> in 1910 and Loewy<sup>4</sup> in 1911. In the former monograph the results of a large number of experiments with the respiration calorimeter of Wesleyan University are gathered in numerous tables. During the so-called rest experiments, however, the subjects were allowed to move about the room and indulge in minor muscular activities, something which had

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1. Benedict and Cathcart: Muscular Work, Carnegie Institution of Washington, 1913, Pub. 187.

2. Lusk: Calorimetric Observations, Med. Rec., New York, 1912, lxxxii, 925; Williams, Riche and Lusk: Animal Calorimetry, Second Paper. Metabolism of the Dog Following the Ingestion of Meat in Large Quantity, Jour. Biol. Chem., 1912, xii, 349; Lusk: Third Paper, Metabolism After the Ingestion of Dextrose and Fat, Including the Behavior of Water, Urea and Sodium Chlorid Solutions, Ibid., 1912, xiii, 27; Lusk: Fifth Paper, The Influence of the Ingestion of Amino-Acids upon Metabolism, Ibid., 1912, xiii, 155; Lusk: Sixth Paper, The Influence of Mixtures of Foodstuffs Upon Metabolism, Ibid., 1912, xiii, 185.

3. Benedict and Carpenter: The Metabolism and Energy Transformations of Healthy Man During Rest, Carnegie Institution of Washington, 1910, Pub. 126.

4. Loewy: Oppenheimer's Handbuch der Biochemie der Menschen und der Thiere, Jena, 1908, iv,<sup>1</sup> 172.

been permitted in practically all the large respiration chambers. Benedict and Carpenter measured the increased heat production caused by certain simple movements which their subjects had performed during the experiments. The act of rising from a chair, taking one or two steps, opening the food aperture, removing the food, closing the window and returning to the chair required only 19 to 29 seconds, but involved the expenditure of 1.22 calories. Considering the short time involved in the operation, the heat production was increased from 200 to 300 per cent. They also found the metabolism 15 per cent higher when the subject was standing than when he was sitting, and from 8 to 10 per cent. higher when lying awake than when sleeping. The sleeping periods were between 1 a. m. and 7 a. m., and the waking periods followed immediately in the three experiments which were really satisfactory. During the waking periods there was an increase in the oxygen consumption amounting to 1.7, 0.9 and 11.5 per cent., while the heat production was increased 5.8, 15.2 and 13.1 per cent. Some of this increase may be accounted for by difference in the time of day, some by small muscular movements. Johansson<sup>5</sup> found that with complete muscular relaxation the carbon dioxid production was the same as during sleep. The two individuals (H. C. K. and H. R. D.) studied by Benedict and Carpenter produced during sleep 35.2 and 36.2 calories per square meter of body surface, whereas only three of the twelve normal men, whose metabolism is recorded in Table 3, produced more than 35.1 calories per square meter per hour. It is obvious that if the metabolism of H. C. K. and H. R. D. were increased 5.8 per cent., 15.2 per cent. and 13.1 per cent., this increase would carry them just so much farther into the zone where it is necessary to assume muscular activity to account for the abnormally high metabolism.

In anticipation it may be well to mention that the average basal heat production of the individuals we are reporting is 34.7 calories per square meter per hour, the subjects lying awake, at perfect rest during the morning hours. The average heat production of the nineteen subjects of Benedict and Carpenter while asleep between the hours of 1 a. m. and 7 a. m. was 35.3 calories and of fifty-five individuals while awake and moving from time to time in the calorimeter was 49.2 calories per square meter per hour. The fact that their sleeping subjects showed a metabolism 3 per cent. higher than our subjects awake may substantiate the conclusions of Johansson. Benedict and Carpenter pointed out at the conclusion of their monograph (p. 246) the fact that the figure 49.2 calories per square meter per hour, equaling

5. Johansson: Ueber die Tageschwankungen des Stoffwechsels und der Körpertemperatur in nüchternem Zustande und vollständige Muskelruhe. Skand. Arch. f. Physiol., 1898, viii, 85.

36.5 calories per kilogram per day, represented not the condition of true rest, but rather that of a person confined for the day to a small room but allowed to dress and undress, sit in a chair, feed himself, etc.

Since the appearance of this monograph Benedict and his coworkers, and also other investigators, have insisted more and more strongly on the necessity of absolute quiet in rest experiments and as a check on muscular activity a graphic record of all movements. This eliminates for our purposes practically all the work done in large respiration chambers before 1910 and leaves us only the work done by means of the small types of apparatus, and especially the Zuntz-Geppert apparatus, by Magnus-Levy and Falk,<sup>6</sup> and by Loewy. The results of the determinations on nineteen normal individuals have been collected in a table by Loewy<sup>7</sup> which is reprinted by Benedict and Joslin.<sup>8</sup> Coleman and DuBois,<sup>9</sup> in gathering normal controls to compare with their typhoid patients, grouped these cases of Loewy with twenty-seven normal controls taken from the work of Benedict and Joslin, and with two of their own cases. The average heat production of the total forty-eight normal men was 33.7 calories per square meter of body surface per hour. Very recently Benedict, Emmes, Roth and Smith<sup>10</sup> published a brief report of their important work on the basal metabolism of a total of eighty-nine men and sixty-eight women. The early appearance of these determinations has been of great service to us, and we wish to express our appreciation to these investigators for the publication of the most essential part of their data.\* All their determinations were made on healthy subjects in the morning at least twelve hours after the last meal, with the subject at complete rest. Some of the experiments were made in the bed calorimeter of the Nutrition Laboratory of Boston, but most of them were short experiments made with the small Benedict "universal respiration apparatus." The fact that this small machine gives results almost identical with the calorimeter was amply proved by Benedict<sup>8</sup> and his coworkers and confirmed by the limited amount of work done with both types of apparatus by

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6. Magnus-Levy and Falk: *Der Lungengaswechsel des Menschen in verschiedenen Alterstufen*, Arch. f. Anat. u. Physiol., 1899, Supp. 314.

7. Loewy: Oppenheimer's *Hand. der Biochemie der Menschen und der Thiere*, Jena, 1908, iv,<sup>1</sup> 179.

8. Benedict and Joslin: *Metabolism in Diabetes Mellitus*, Carnegie Institution of Washington, 1910, Pub. 136; *A Study of Metabolism in Severe Diabetes*, *ibid.*, 1912, No. 176. *Ueber der Stoff- und Energieumsatz bei Diabetes*, Deutsch. Arch. f. klin. Med., 1913, cxi, 333.

9. Coleman and DuBois: *The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever*, *THE ARCHIVES INT. MED.*, 1914, xiv, 168.

10. Benedict, Emmes, Roth and Smith: *The Basal, Gaseous Metabolism of Normal Men and Women*, *Jour. Biol. Chem.*, 1914, xviii, 139.

\*A more complete discussion of the work is appearing in the *Jour. Biol. Chem.*, March, 1915.



Coleman and Du Bois.<sup>9</sup> The average heat production of the eighty-nine men was 34.7 calories per square meter per hour, and of the sixty-eight women, 32.2 calories. The lower heat production of women is in accord with the previous findings of Sonden and Tigerstedt.<sup>11</sup>

The work of Magnus-Levy and Falk<sup>6</sup> showing the diminution of metabolism in old age and the increase in youth is also confirmed. The two men over 50 years of age produced only 28.9 calories per square meter. The eight youths between 17 and 20 averaged 37.1 calories, nine who were 20 years old, 36.6 calories, seven who were 21 years old, 36.1 calories.

#### SPECIFIC DYNAMIC ACTION OF FOODS

The subject of the specific dynamic action of foods in increasing metabolism is fully discussed by Lusk<sup>12</sup> in his text-book and in a series of papers on animal calorimetry.<sup>2, 13</sup>

From his work on dogs, Lusk has concluded that the specific dynamic action of protein is due to the stimulation of the metabolism of the cells by certain of the amino-acids while the action of fat and carbohydrates is due to the mass action of these metabolites in the circulation. He has found marked differences in the action of the various amino-acids and the various carbohydrates. The study of the specific dynamic action of foods on man is not nearly as far advanced as in the case of the dog. Magnus-Levy<sup>14</sup> in connection with his work on dogs found that after giving a man 50 to 60 grams of carbohydrate the metabolism was increased in the first hour from 2 to 12 per cent., in the second hour 0 to 7 per cent. After 140 to 160 grams of starch in bread the increase in the first hour averaged 22 per cent., the second hour 14 per cent., the third hour 16 per cent. After 210 grams of bacon and butter the metabolism was increased 5 to 10 per cent. for seven to eight hours, while after 210 to 250 grams of beef the oxygen consumption rose from 3 to 12 per cent. the first hour and then 15 to 34 per cent. in the next six hours. Gigon<sup>15</sup> obtained similar results using a Jacquet apparatus. In the period of four to five hours following the ingestion of 100 grams of dextrose there was an increase of 9.5 per cent. in the oxygen consumption. After 50 grams of casein the oxygen was increased 5.5 per cent. and after 100 grams 16.8 per cent.

11. Sonden and Tigerstedt: Untersuchungen über die Respiration und den Gesamtstoffwechsel des Menschen, Skand. Arch. f. Physiol., 1895, vi, 99.

12. Lusk: The Science of Nutrition, Philadelphia, 1909, second edition; Stoffwechsel und Ernährung, Deutsche Übersetzung von L. Hess, 1910.

13. Lusk: The Cause of the Specific Dynamic Action of Protein, THE AMERICAN JOURNAL OF MEDICINE, 1913, xxi, 485.

14. Magnus-Levy: Ueber die Grösse des respiratorischen Gaswechsels unter dem Einfluss der Nahrungsaufnahme, Arch. f. d. ges. Physiol. (Pflüger's), 1884, iv, 1.

15. Gigon: Ueber den Einfluss der Nahrungsaufnahme auf den Gaswechsel und Energieumsatz, Arch. f. d. ges. Physiol. (Pflüger's), 1911, cxl, 500.

## EXPERIMENTAL PROCEDURE

The normal controls who were kept in the metabolism ward were given a maintenance ration, the last meal of the day being about 5 p. m. At 5 a. m. they were awakened, given an enema, and instead of breakfast, a cup of coffee without cream or sugar. At about half past nine the calorimeter bed was wheeled to the ward on the weighing platform, which is provided with large casters, and the subject lifted from his bed, weighed, rolled back to the calorimeter room and slid into the calorimeter, bed and all. He was dressed in a night shirt, thick ward pajamas and thick socks, and, as a rule, the legs were covered with a sheet, although some subjects needed a thin blanket and others required no covering. A soft pillow was placed under the head and sometimes one under the knees. Every effort was made to ensure absolute comfort, a matter of great importance in work on the respiratory metabolism.

Those normal controls who lived at home took their evening meal at 6 or 7 o'clock, rose at 6 or 7 a. m., drank a cup of black coffee, took the street car, walked about  $\frac{1}{4}$  mile and arrived at the hospital at 9 o'clock. They then undressed, weighed themselves, dressed in warm pajamas and entered the calorimeter.

As soon as the subject was in the calorimeter the rectal thermometer was inserted about 12 cm. in the rectum, giving slight discomfort for a few minutes, but later remaining in position without the man's being conscious of its presence. The surface thermometers were next fastened tightly to the thorax, axillae or abdomen by means of adhesive plaster and the whole covered with a pad of absorbent cotton about 20 cm. in diameter and 3 or 4 cm. thick, this being held in place by strips of adhesive. The Bowles stethoscope was next strapped over the apex of the heart and the whole covered with night shirt and pajamas. When this was finished the bed was shoved all the way into the box, the ventilation started, and at about a quarter past 10 the glass plates were sealed in the end of the calorimeter and the heavy front put in position, making it possible to start the preliminary period shortly after half past ten.

The actual preparation of the calorimeter had begun long before this. On the previous afternoon all sulphuric bottles, soda-lime containers, etc., had been filled and the oxygen tank weighed so that any leakage over night might be detected. The temperature of the calorimeter room had been watched every hour by the night nurse and maintained within 1 degree of the standard experimental temperature of 23 C. At nine in the morning the water circulation through the various cooling coils and the absorber had been started and a lighted 32 candle power electric lamp placed in the box until the subject was ready. If

these precautions had been carefully followed and if the observer had watched the temperature of the various parts of the apparatus, it was possible to bring the box into perfect equilibrium and control fifteen to twenty minutes after the start of the preliminary period. As we shall see later, there is reason to believe that during the first hour after the box is sealed the wooden frame of the bed may absorb a little heat owing to its proximity to the subject's body.

As a rule the preliminary period lasts thirty to forty minutes and the experiment begins shortly after 11 o'clock. Eight minutes before the start a sign is hung in the window telling the subject to remain absolutely quiet and the first residual sample of ten liters of air is drawn through U tubes by means of the Bohr meter. At four or five minutes before the start the second residual is begun and a tracing of the spirometer curve made in the manner first used by Benedict and Carpenter. At "time" the various cocks and switches are turned

TABLE 1.—THE STATISTICS OF THE NORMAL CONTROLS

Subject	Weight, Kg.	Height, Cm.	Chest Circumference, Cm.	Age, Yrs.
G. L. ....	78.4	175.5	90.5	47
E. F. D. B. ....	73.6 73.5	178.8	91.5	31-32
F. C. G. ....	56.5	173.9	80.2	29
R. H. H. ....	62.0	177.2	85.3	21
L. C. M. ....	56.5	170.6	86.6	22
Louis M. ....	51.7	.....	.....	22
John L. ....	70.9	.....	.....	44

as described in the previous article. One or two minutes after "time" the subject is allowed to shift his position, and, if necessary, void into a tared urine bottle which he then places on a small spring balance so that the exact weight of urine passed can be read through the calorimeter window. During the remainder of the hour he lies as quiet as possible trying not to turn from back to side and vice versa more than once an hour. The work-adder on the spirometer records each movement and the electrical control of the calorimeter is so delicate that the observer in charge of the thermometers can detect such slight activity as turning the head to look out of the window by the rise in the temperature of the air and wall. At the close of the first and subsequent hours the procedure is the same as at the start, except that only one sample of residual air is analyzed.

The statistics of the normal controls are as shown in the accompanying table (Table 1).

## DESCRIPTION OF SUBJECTS AND DETAILS OF EXPERIMENTS

G. L., physiologist, large frame, slightly adipose. Has taken but little exercise during the last few years. Health good, no recent illnesses. Physical examination negative.

*Experiment 1.*—March 11, 1913. Although this was the first experiment on man made with the Sage calorimeter, the accuracy of the machine had been thoroughly tested by means of the alcohol checks described in Paper 2. The temperature of the air in the calorimeter was 24.5 C. in this experiment instead of the temperature of 23 C. used later. In addition to a suit of pajamas, the subject wore a heavy sweater. The basal metabolism was determined in the first two hours and at the beginning of the third hour he drank a solution of 115 grams commercial glucose (dextrose 42.37 per cent., dextrin 44.57 per cent., water 13.50 per cent.) in 500 c.c. water and 10 c.c. lemon juice. The commercial glucose was equivalent in calories to 100 grams dextrose. The subject, who had felt somewhat too warm during the first two hours, perspired profusely after the glucose. He remained very quiet during the five hours.

E. F. D. B., physician, large frame, moderate adipose. Up to the age of 22 in good athletic condition; since then has exercised in steadily decreasing amounts. During the winter of 1913 took violent exercise for about half an hour twice a week; in 1914 scarcely exercised at all. General health good; no recent illnesses. Heart, lungs, etc., normal.

*Experiment 2.*—March 13, 1913. The basal metabolism was determined in the first two hours, and at the beginning of the third hour he drank 115 grams commercial glucose in the same solution as in the experiment on G. L. The temperature of the calorimeter was 22 C. and his clothing consisted of thin undershirt and pajamas. He did not perspire but blew his nose several times each hour, spent a good deal of the time looking out of the window and was distinctly more restless than in the subsequent observations.

*Experiment 25.*—May 17, 1913. Basal determination only. Was very quiet during all three hours and dozed from 11:30 to 11:50.

*Experiment 27.*—May 22, 1913. At 8:55 a. m., before entering the calorimeter, drank 230 gm. commercial glucose (equivalent to 200 gm. dextrose) in 500 c.c. water and 15 c.c. lemon juice. Six minutes were required to drink the mixture. Dozed at times during the experiment.

*Experiment 115.*—March 30, 1914. Basal metabolism only. This experiment was conducted by only two observers, Mr. Soderstrom and Mr. Harries, and the periods were made one and one-half hours long to give them more time for weighings, etc. In the subsequent experiments on this subject these two observers alone were able to make all measurements and keep up with the calculations in hourly periods, a record of which they may well be proud, especially since the agreement between the direct and indirect calorimetry was unusually good.

*Experiment 116.*—April 1, 1914. Just before entering the calorimeter between 9:45 and 10:07 a. m., the subject ate the following meal containing 10.5 gm. nitrogen: fat-free milk, 600; pot cheese (cottage cheese or *Schmierkäse*), 150; egg-white, 120; egg-yolk, 20. During this experiment the work-adder was out of order and recorded part of the excursions of the spirometer due to the admission of oxygen to the box. The subject was very quiet, much more quiet than the work-adder record would indicate.

*Experiment 138.*—May 8, 1914. Between 10:05 and 10:07 a. m., drank a solution of 200 gm. C. P. Dextrose (Merck) in 400 c.c. water and 35 c.c. lemon juice. No glycosuria resulted in this or any other of the experiments on normal controls.

*Experiment 141.*—May 15, 1914. An attempt was made to raise the respiratory quotient as high as possible by filling the glycogen stores of the body

before giving the dextrose. At 11:30 the night before the experiment and again at 6:15 in the morning the subject ate the following carbohydrate meal: shredded wheat, 55 gm.; milk, 100 c.c.; cane sugar, 10 gm.; in the morning taking an additional 10 gm. cane sugar in coffee. Between 9:50 and 9:53 he drank a solution of 200 gm. C. P. Dextrose in 400 c.c. water and 35 c.c. lemon juice.

F. C. G., chemist, thin. At age of 16 had an attack of malaria lasting two weeks. Has not been sick in bed since then and has never weighed over 64 kg. (140 pounds). Has never taken systematic exercise, except baseball from 1900 to 1906. Appetite fair, sleeps well. Physical examination: complexion pale and somewhat sallow; hemoglobin normal; state of nutrition rather poor; heart, lungs and abdomen normal. Experiment 142, May 18, 1914. Basal determination.

*Experiment 3.*—March 17, 1913. The basal metabolism was determined between 9:02 and 12:02, the subject going into a profound sleep in the second and third hours. The calorimeter was then opened and the subject ate the *Haferschleim* mixture of Schmidt's test diet. This contained 40 gm. dry oatmeal, 10 butter, 200 milk and one egg, or approximately, protein, 13.1, fat, 10.2, carbohydrate, 35.5 gm. At the end of the observation it was apparent that the respiratory quotients were abnormally low and that the apparent oxygen consumption was much higher than was consistent with the direct calorimetry. The cause for this was found in a leak in the oxygen cylinder, making it necessary to omit the oxygen figures from the data and base the calculations on the direct calorimetry alone.

*Experiment 17.*—April 22, 1914. Basal determination. The subject remained very quiet, but took care not to go to sleep. Unfortunately the oxygen cylinder leaked again and the calculation of the indirect calorimetry was not accurate.

R. H. H., chemist, tall and spare with long and rather thin bones, very little adipose. At the age of 12 had pneumonia, since then always well. Up to four years ago played semiprofessional baseball or basketball almost every day. Since 1910 his exercise has been limited to four to ten miles of walking a day and in summer a swim of about two miles a day. Physical condition good, heart, lungs and abdomen normal.

*Experiment 4.*—March 13, 1913. Basal determination. During the experiment this subject tried to void at the beginning of each hour but was unable to do so and was slightly more nervous and more active than the other subjects. He could not void before his first meal after the experiment and it has therefore been necessary to omit the figures for the urinary nitrogen and base the calculations on the tables of Magnus-Levy,<sup>16</sup> assuming that 15 per cent. of the calories were derived from protein.

Louis M., barber, small frame, short and thin, muscles fairly firm. This subject was in the hospital from September 7 to October 30, 1912, with a moderately severe attack of typhoid fever, and served as a subject of numerous observations by means of the Benedict universal respiration apparatus (Coleman and DuBois<sup>17</sup>). He was born in Germany and came to New Orleans in 1911. There he suffered from a severe attack of malaria but has had no recurrences. His family history shows that one sister is insane.

After his attack of typhoid he left the hospital in excellent condition and he has been perfectly well for the last four months, although at first he was somewhat weak and easily tired. Physical examination shows heart, lungs, abdomen, etc., to be normal.

*Experiment 7.*—March 26, 1913. Basal metabolism. Subject remained in the metabolism ward four days. On the evening previous to this experiment

16. Magnus-Levy: Von Noorden's Handbuch der Pathologie des Stoffwechsels. Ed. 2, 1906.



at 5 p. m., ate a dinner containing protein, 35.1 gm., fat, 37.1. carbohydrate, 105.6. During the experiment he lay very quiet, dozing most of the time.

*Experiment 8.*—March 28, 1913. March 27 his food contained protein, 80.6; fat, 168.9; carbohydrate, 268.7 gm.; the last meal of the day at 6 p. m. containing protein, 28.9; fat, 61.7; carbohydrate, 82.3 gm. Just before entering the box, between 8:25 and 9:25 a. m., he ate 725 gm. chopped beef, fried in butter, the whole containing 23.93 gm. nitrogen and 100 gm. fat. During the experiment he slept from 12:26 to 1:18 p. m. and from 3:22 to 3:30. There was a small leak from the absorber pipe into the calorimeter, making the apparent water elimination about 1 gram an hour too high.

John L., dentist, medium frame, medium height, well nourished, muscles flabby. This subject, who was born in Sweden, served as a normal control in the metabolism experiments of Dr. R. A. Cooke,<sup>17</sup> who investigated the functional powers of the kidneys. Careful tests showed in this subject a slight delay in the excretion of sodium chlorid, but there were no other signs of kidney disease. He gave a history of moderate indulgence in alcohol. In 1904 he was jaundiced; a few months prior to the experiment he suffered from an infected hand after a dog bite. For the last five years he has been nervous. He was admitted to the hospital Jan. 15, 1914, suffering from a few small boils and a pedicular eruption. His ailments were so slight that he was induced to remain in the hospital as a normal control and, being without a home, he was glad to remain. Physical examination showed a thorax with flaring ribs and an increased anteroposterior diameter of the chest with hyperresonant percussion note and breath sounds somewhat distant. The teeth were in poor condition; blood-pressure, systolic 115 to 130, diastolic 75 to 90.

*Experiment 113.*—March 26, 1914. Basal metabolism. During the previous day the diet had contained 11.5 gm. KCl and a minimum of NaCl. The last meal at 6 p. m. had consisted of farina, 25; egg-white, 50; yolk, 50; sugar, 50; cream (20 per cent. fat), 60; KCl, 3.5 gm. Blood-pressure March 25, systolic, 140; diastolic, 95; just before the calorimeter experiment, systolic 135, diastolic 105.

L. C. M., laboratory helper, small frame, somewhat short and thin. He was born in Sicily where he lived until the age of 11. Shortly before leaving for this country he suffered from malaria, but since then has been in good health. For the last five years he has worked in the daytime and gone to school at night, consequently has taken but little exercise. Heart, lungs and abdomen normal.

*Experiment 136.*—May 4, 1914. Basal metabolism.

*Experiment 137.*—May 6, 1914. Between 9:50 and 9:53 drank a solution of 200 gm. C. P. dextrose in 400 c.c. water and 35 c.c. lemon juice. No glycosuria.

The subjects have been described in detail above and particular attention has been given to the athletic history, since the recent work in Benedict's laboratory (personal communication) has shown a difference in the metabolism of athletes and non-athletic individuals. From a study of the results in previous determinations of the normal metabolism one is led to suspect that a few distinctly abnormal cases have crept in. It has, therefore, been our practice to give the normal controls as careful physical examination as the patients. The importance of this is manifest if one considers that the onset of hyperthyroidism is usually accompanied by the symptoms of exuberant good health.

17. Cooke: Unpublished.



The details of the individual experiments are given below. The body weight at the start of the experiment is determined by weighing the subject shortly before he enters the calorimeter and then making the proper corrections for food, urine and insensible perspiration. All calculations are made from this weight, the surface area being reckoned from Meeh's<sup>18</sup> formula  $12.312 \sqrt[3]{WT^2}$ . Some actual determinations of the surface area of E. F. D. B. have shown that Meeh's formula is 14.3 per cent. too high in his case, while it is only 7.3 per cent. too high in the case of R. H. H. Calculated from a new formula, Meeh's figures are 14.5 per cent. too high in the case of G. L., 9.3 per cent. too high in the case F. C. G. and 13.4 per cent. too high in the case of L. C. M. These measurements will be given in detail in a subsequent paper. For purposes of uniformity, however, calculations are based on Meeh's formula, since this has been used in all other metabolism work. The work-adder was not attached to the calorimeter until May 16, 1913, and an exact record of the activity of the subjects was not obtained before this date. After the work-adder as described in Paper 2 was attached it was possible to compare the activity in different periods and in different experiments and express this in terms of the number of centimeters that the plummet was raised by the expansion of air within the box. The excursion of the plummet for certain movements of the subject was roughly calculated as follows: Raising arm to head, 0.3 cm.; lifting telephone to mouth, 4 cm.; turning from back to side, 7 cm.

In the tables the final calculations of calories per hour have been based on the indirect calorimetry as calculated from the oxygen consumption and the respiratory quotient. In the two experiments on F. C. G., where these were inaccurate the direct calorimetry was used, and in one of the hours in the experiment on G. L. where the CO<sub>2</sub> measurement was lost the non-protein R. Q. for the purposes of calculation was assumed to be 1.00.

In the experiments on E. F. D. B. on May 22 there was an evident error in the division of oxygen between the second and third and the fourth and fifth periods, so these were averaged in the final calculations.

The methods of calculation have been described in Paper 1, but it may be well to remind the reader that the method of direct calorimetry represents the heat eliminated from the body, plus or minus the heat stored in or lost from the body, when the temperature of the body rises or falls. The calculation of the percentage of calories derived from protein, fat and carbohydrate is based on the urinary nitrogen and the non-protein respiratory quotient.

18. Meeh: Oberflächenmessungen des menschlichen Körpers, Ztschr. f. Biol., 1879, xv, 425.

TABLE 2.—EXPERIMENTAL—

Subject Date	Weight Kg.	Period	End of Period	CO <sub>2</sub> , Gm.	O <sub>2</sub> , Gm.	R. Q.	H <sub>2</sub> O, Gm.	Urine N Per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.
G. L. .... 3/11/13	78.42	Preliminary	A. M. 9:50							
		1st Hr. ....	10:50	25.26	21.51	0.85	37.03	0.487	72.35	76.77
		2d Hr. ....	11:50	26.56	25.90	0.75	37.84	0.487	84.85	86.10
		1st Hr. P. C.	P. M. 12:50	29.61	28.57	0.75	37.88	0.404	94.12	87.75
		2d Hr. P. C.	1:50	.....	25.75	.....	39.24	0.404	86.76*	92.53
		3d Hr. P. C.	2:50	30.33	23.44	0.94	38.98	0.404	80.86	95.67
E. F. D. B. 3/13/13	73.6	Preliminary	A. M. 9:35							
		1st Hr. ....	10:35	27.22	25.27	0.78	27.91	0.554	83.52	77.85
		2d Hr. ....	11:35	25.28	21.32	0.86	26.53	0.554	71.75	71.94
		1st Hr. P. C.	P. M. 12:35	29.51	23.58	0.91	31.19	0.621	80.27	84.87
		2d Hr. P. C.	1:35	31.12	25.50	0.89	30.50	0.621	86.42	82.87
		3d Hr. P. C.	2:35	30.30	24.94	0.88	30.40	0.621	84.41	81.46
E. F. D. B. 5/17/13	75.51	4th Hr. P. C.	3:35	29.92	24.10	0.90	32.02	0.621	81.92	86.02
		Preliminary	A. M. 9:30							
		1st Hr. ....	10:30	25.41	22.37	0.83	34.22	0.526	74.69	76.83
		2d Hr. ....	11:30	25.45	21.95	0.84	32.00	0.526	73.60	76.67
		3d Hr. ....	P. M. 12:30	25.00	21.24	0.86	30.68	0.526	71.41	74.13
		Preliminary	A. M. 9:30							
E. F. D. B. 5/22/13	76.10	2d Hr. P. C.	19:30	31.13	23.04	0.98	36.24	0.581	79.77	84.61
		3d Hr. P. C.	11:30	31.53	25.29	0.97	36.13	0.581	165.30	83.21
		4th Hr. P. C.	P. M. 12:30	32.45	22.49		35.07	0.581		83.91
		5th Hr. P. C.	1:30	31.95	28.84	0.95	36.63	0.581	162.04	84.45
		6th Hr. P. C.	2:30	29.73	18.18		36.78	0.581		84.96
		Preliminary	A. M. 11:25							
E. F. D. B. 3/30/14	74.34	1½ Hrs. ....	P. M. 12:55	36.10	32.26	0.81	45.08	0.518	107.30	113.13
		1½ Hrs. ....	2:25	37.58	34.88	0.78	46.48	0.518	115.24	113.14
		Preliminary	A. M. 11:27							
E. F. D. B. 4/1/14	74.92	2d Hr. P. C.	P. M. 12:27	27.47	24.30	0.82	30.51	0.856	80.50	81.65
		3d Hr. P. C.	1:27	29.66	26.17	0.83	31.75	0.830	86.91	81.50
		4th Hr. P. C.	2:27	28.13	25.35	0.81	32.87	0.900	83.60	85.08
		5th Hr. P. C.	3:27	28.83	25.89	0.81	33.39	0.577	86.11	82.75
		6th Hr. P. C.	4:27	27.12	23.86	0.83	32.98	0.577	79.61	83.63
		Preliminary	A. M. 11:05							
E. F. D. B. 5/8/14	74.75	2d Hr. P. C.	P. M. 12:05	30.55	23.41	0.95	32.59	0.604	80.53	76.35
		3d Hr. P. C.	1:05	30.91	24.28	0.93	33.55	0.604	83.08	79.08
		4th Hr. P. C.	2:05	29.37	22.49	0.95	32.48	0.604	77.33	75.63
		5th Hr. P. C.	3:05	30.28	22.06	1.00	32.22	0.604	76.47	76.46
		Preliminary	A. M. 10:50							
E. F. D. B. 5/15/14	75.02	2d Hr. P. C.	11:50	29.60	22.01	0.94	29.06	0.534	78.74	77.70
		3d Hr. P. C.	P. M. 12:50	31.35	22.12	1.03	30.02	0.534	77.26	80.00
		4th Hr. P. C.	1:50	31.07	24.04	0.94	30.73	0.534	82.67	80.20
		5th Hr. P. C.	2:50	29.95	22.21	0.98	30.87	0.534	76.96	79.90
		6th Hr. P. C.	3:50	28.46	22.57	0.92	30.46	0.534	77.11	75.00
		Preliminary	A. M.							

# DATA IN HOURLY PERIODS

Direct Cal.	Rectal Temperature, C.	Av. Pulse	Work-Adder, Cm.	Non-Protein R. Q.	Per Cent. Calories from			Calories Per Hour		Remarks
					Prot.	Fat	Carb.	Per Kg.	Per Sq. M.	
	37.26									
2.95	37.30	..	....	0.87	18	37	45	0.92	32.07	Basal.
2.90	37.25	62	....	0.74	15	77	8	1.08	37.61	Basal.
4.21	37.28	88	....	0.75	11	77	12	1.20	41.72	At 11:53 a. m., 115 gm. commercial glucose.
6.54	37.20	..	....	....	12	..	..	1.11*	38.46*	
2.88	37.17	..	....	0.86	13	11	76	1.03	35.84	
	36.88									
28.02	36.90	..	....	0.78	18	62	20	1.13	38.63	Basal.
22.10	36.91	59	....	0.88	20	83	47	0.98	33.19	Basal.
27.12	36.84	57	....	0.94	21	16	63	1.10	37.13	At 11:38 a. m., 115 gm. commercial glucose.
33.46	36.87	64	....	0.91	19	25	56	1.18	39.97	
35.00	36.98	..	....	0.91	19	26	55	1.15	39.04	
34.64	36.99	60	....	0.93	20	19	61	1.11	37.89	
	36.96									
62.89	36.81	57	22	0.83	19	47	34	0.99	33.95	Basal.
77.00	36.80	55	13	0.85	19	41	40	0.97	33.45	Basal.
74.42	36.98	..	10	0.87	19	36	45	0.95	32.46	Basal.
	36.84									At 8:55 a. m., 230 gm. commercial glucose.
72.60	36.75	66	15	1.03	19	0	81	1.05	36.08	
82.51	36.84	63	17	1.02	19	0	81	1.09	37.38	
84.53	36.96	60	14							
82.50	37.01	58	16	0.99	19	2	79	1.07	36.64	
79.32	37.00	60	24							
	36.91									
110.72	36.88	54	30—	0.82	19	51	30	0.96	32.86	Basal.
116.62	36.99	56	37—	0.78	18	62	20	1.05	35.29	Basal.
	36.84									At 9:54 a. m., protein meal (10.5 gm. N).
51.05	36.91	57	24—	0.83	28	42	30	1.07	36.79	
77.92	36.89	57	28—	0.53	25	43	32	1.16	39.72	
86.71	36.93	58	30—	0.51	29	46	25	1.12	38.21	
81.62	36.94	57	26—	0.81	18	53	29	1.15	39.36	
88.88	37.04	58	33—	0.83	19	46	35	1.06	36.39	
	36.69									
75.09	36.67	61	14.1	0.99	20	3	77	1.08	36.86	At 10:05-10:07 a. m., 200 gm. dextrose.
83.22	36.78	61	23.5	0.96	19	11	70	1.11	38.02	
76.01	36.78	61	18.8	0.99	21	2	77	1.03	35.39	
76.05	36.79	62	26.0	1.06	21	..	79	1.02	35.00	
	36.69									
78.82	36.73	55	19.6	0.97	18	8	74	1.05	35.95	At 9:50-9:53 a. m., 200 gm. dextrose.
78.59	36.73	58	22.5	1.09	18	..	82	1.03	35.28	
79.13	36.73	59	33.1	0.97	17	8	75	1.10	37.75	(Carbohydrate breakfast at 6:15 a. m.).
81.22	36.76	59	21.8	1.03	18	..	82	1.03	35.14	
73.36	36.74	57	34.0	0.95	18	15	67	1.03	35.21	

\* Estimated from CO<sub>2</sub>.

TABLE 2.—

Subject Date	Weight kg.	Period	End of Period	CO <sub>2</sub> , Gm.	O <sub>2</sub> , Gm.	R Q.	H <sub>2</sub> O, Gm.	Urine N Per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.
E. F. D. B. 5/18/14	73.70	Preliminary	10:50							
		1st Hr. ....	11:50 P. M.	23.92	21.68	0.83	28.02	0.530	70.29	67.48
		2d Hr. ....	12:50 A. M.	23.85	21.88	0.79	28.08	0.530	72.38	69.37
F. C. G. ... 3/17/13	56.5	Preliminary	9:02							
		1st Hr. ....	10:02	22.80	.....	.....	17.77	0.491	.....	54.43
		2d Hr. ....	11:02 P. M.	22.92	.....	.....	19.09	0.491	.....	59.16
F. C. G. ... 3/17/13	56.5	3d Hr. ....	12:02	22.59	.....	.....	20.90	0.491	.....	60.70
		Preliminary	1:00							
		2d Hr. P. C.	2:00	14.86	41.52	0.85	23.05	0.491	139.35	160.85
F. C. G. ... 3/17/13	56.5	3d Hr. P. C.	3:00	23.53	21.08		30.51	0.491		168.89
		4th Hr. P. C.	4:00 A. M.	22.73	25.27	0.78	26.08	0.491	69.59	62.52
F. C. G. ... 4/22/13	50.82	Preliminary	9:45							
		1st Hr. ....	10:45	21.92	.....	.....	25.40	.....	.....	58.96
		2d Hr. ....	11:45 P. M.	22.05	.....	.....	26.85	.....	.....	61.94
F. C. G. ... 4/22/13	50.82	3d Hr. ....	12:45	21.08	.....	.....	26.26	.....	.....	62.60
		4th Hr. ....	1:45	21.86	.....	.....	28.59	.....	.....	69.33
		5th Hr. ....	2:45 A. M.	22.03	.....	.....	30.09	.....	.....	68.43
R. H. H. ... 3/19/13	62.00	Preliminary	9:42							
		1st Hr. ....	10:42	26.15	21.59	0.88	27.50	.....	73.54	66.50
		2d Hr. ....	11:42 A. M.	27.42	20.98	0.95	28.96	.....	72.78	66.27
Louis M. ... 3/26/13	51.70	Preliminary	10:10							
		1st Hr. ....	11:10 P. M.	20.53	18.73	0.80	28.92	0.522	61.91	64.64
		2d Hr. ....	12:10	19.95	17.40	0.83	26.95	0.522	57.66	64.44
Louis M. ... 3/26/13	51.70	3d Hr. ....	1:10	22.44	20.07	0.81	28.10	0.522	66.57	71.00
		4th Hr. ....	2:10	18.34	18.05	0.74	25.73	0.522	58.71	66.51
		5th Hr. ....	3:10	22.13	20.71	0.78	27.36	0.522	68.50	68.28
Louis M. ... 3/26/13	51.70	6th Hr. ....	4:10 A. M.	19.36	19.23	0.73	26.85	0.522	62.51	67.86
		Preliminary	11:14 P. M.							
		3d Hr. P. C.	12:14	23.43	22.62	0.75	24.08	0.703	73.76	64.89
Louis M. ... 3/26/13	51.70	4th Hr. P. C.	1:14	24.27	22.67	0.78	29.15	0.695	74.44	70.48
		5th Hr. P. C.	2:14	26.84	25.11	0.78	34.80	0.970	82.02	79.07
		6th Hr. P. C.	3:14	26.44	25.11	0.77	34.38	1.014	81.70	77.18
Louis M. ... 3/26/13	51.70	7th Hr. P. C.	4:14	24.85	23.21	0.78	35.42	1.138	75.38	83.35
		8th Hr. P. C.	5:14 A. M.	26.25	24.19	0.77	34.71	1.112	80.53	81.28
John L. .... 3/26/14	70.94	Preliminary	11:20 P. M.							
		1st Hr. ....	12:20	21.12	19.51	0.79	25.77	0.363	64.65	66.00
		2d Hr. ....	1:20	21.37	19.62	0.79	24.56	0.363	65.10	68.26
John L. .... 3/26/14	70.94	3d Hr. ....	2:20 A. M.	21.07	19.97	0.77	24.01	0.363	65.85	66.72
		Preliminary	11:02 P. M.							
		1st Hr. ....	12:02	22.39	20.71	0.79	28.32	0.534	68.34	71.73
L. C. M. 5/4/14	59.70	2d Hr. ....	1:02 A. M.	22.14	18.98	0.85	27.28	0.534	63.57	70.66
		Preliminary	10:52							
		2d Hr. P. C.	11:52 P. M.	22.04	20.79	0.92	30.43	0.578	81.05	79.94
L. C. M. 5/4/14	59.70	3d Hr. P. C.	12:52	20.20	22.03	1.00	32.38	0.578	76.45	74.95
		4th Hr. P. C.	1:52	20.65	21.60	1.02	32.94	0.578	76.21	77.07

Direct Calorimetry Cal.	Rectal Temperature, C.	Av. Pulse	Work-Adder, Cm.	Non-Protein R. Q.	Per Cent. Calories from			Calories Per Hour		Remarks
					Prot.	Fat	Carb.	Per Kg.	Per Sq. M.	
	36.76									
67.14	36.76	57	18.2	0.83	20	46	34	0.95	32.48	Basal.
70.23	36.78	57	18.2	0.79	19	58	23	0.98	33.45	
	37.03									
58.82	37.15							1.04	30.75	Basal. Profound sleep during second and third periods. O <sub>2</sub> leak.
55.75	37.11							0.99	32.45	
56.99	37.06							1.01	31.43	
	37.02									
66.55	37.17			0.86	19	39	42	1.18	36.87	At 12 m., plate of oatmeal. O <sub>2</sub> leak.
60.23	37.00							1.107	33.29	
66.82	36.95			0.78	19	61	20	1.08	33.50	
	37.04									
57.28	37.03	71						1.04	32.22	Basal. O <sub>2</sub> leak.
56.68	37.07	68						1.14	35.25	
62.00	37.01	64						1.10	34.03	
58.15	36.94	66						1.06	32.71	
61.88	36.87	70						1.18	36.40	
	36.76									
59.97	36.82							1.19	33.12	Basal. Urine not obtained.
56.31	36.85							1.19	37.73	
	37.18									
58.29	37.07			0.80	22	56	24	1.20	36.23	Basal.
61.48	37.04			0.84	24	40	36	1.12	33.92	
55.26	37.15			0.82	21	49	30	1.29	38.95	
59.27	37.00			0.72	24	73	3	1.14	34.35	
56.95	37.03			0.77	20	63	17	1.32	39.91	
65.17	36.98			0.81	23	77	1	1.21	36.58	
	37.10									
54.80	37.28			0.74	25	68	7	1.39	42.50	8:25-9:25 a. m., 725 gm. chopped beef = 23.93 gm. N + 100 gm. fat.
51.49	37.43			0.77	25	56	16	1.40	42.59	
51.67	37.39			0.76	24	55	14	1.54	46.92	
52.46	37.41			0.75	23	58	9	1.54	46.74	
50.66	37.38			0.76	40	40	11	1.42	43.12	
51.90	37.36			0.75	37	54	9	1.51	46.07	
	37.10									
52.70	36.80	65	13.0+	0.78	25	62	23	0.91	30.64	Basal.
58.24	36.84	52	13.0+	0.79	25	61	24	0.92	30.85	
56.54	36.88	67	12.7	0.76	25	60	15	0.92	31.21	
	37.04									
52.55	36.65	74	22.0+	0.78	21	50	29	1.15	36.41	Basal.
53.48	36.92	70	18.2	0.86	22	37	41	1.07	33.87	
	36.84									
55.71	36.70	85	19.1	0.95	19	55	26	1.33	42.48	9:50-9:53 a. m., dextrose, 200 gm.
50.60	36.68	82	20.1	1.06	20			1.25	40.07	
50.00	36.79	79	35.2	1.08	20			1.25	39.94	

The results are expressed in terms of grams and calories per hour, since this is the length of period used in the Cornell and Sage calorimeters and is the nearest unit of the length of the actual experimental period used in most of the modern machines.

#### DISCUSSION OF RESULTS

As explained in Paper 1 of this series, the determination of the heat production by the methods of direct and indirect calorimetry have been found to give identical results in the work of Rubner, Atwater and Benedict, Lusk and his coworkers. Rubner demonstrated this on the dog in long periods, Atwater and Benedict on man at rest and at work, Lusk on dogs in hourly periods and Howland, in Lusk's laboratory, on babies both normal and atrophic. To this list may be added the work of Armsby<sup>19</sup> on cattle in twenty-four-hour experiments and the work of Carpenter and Murlin<sup>20</sup> who studied the metabolism of women before and after confinement, in Benedict's laboratory. A comparison of the figures for direct and indirect calorimetry obtained in Benedict's calorimeter shows excellent agreement in the two- and three-hour periods. Out of a total of twenty-eight periods, the two methods were within 5 per cent. of each other in seventeen, while only six showed a disagreement over 10 per cent.

Table 3 gives in parallel columns the calories in each of our experiments as measured by the methods of direct and indirect calorimetry. The totals of all the experiments show that the two methods come within 0.17 per cent. of each other. Even when we consider periods as short as one hour, the agreement may be striking. On the normal control, E. F. D. B., there were a total of 26 one-hour periods. In 17 of these the methods of direct and indirect calorimetry agreed within 5 per cent., in 6 periods within 6 to 9 per cent., while three isolated periods showed a disagreement of 11, 12 and 16 per cent., respectively. Work with the Sage calorimeter on normal controls and on patients with a large variety of diseases has shown that in a total measurement of 27,632 calories the direct calorimetry gives a figure only 1.62 per cent. lower than the indirect. There is, therefore, no reason to believe that in long periods, or in the average of a number of short periods, there is any essential difference between the two methods. As will be shown later, there is good reason to believe that indirect calorimetry gives the more accurate results in short periods.

There are two methods of calculating the indirect calorimetry, both of which involve factors that change with the respiratory quotient.

19. Armsby: Food as Body Fuel, Pennsylvania State College Agricultural Experiment Station, Bull. 126.

20. Carpenter and Murlin: The Energy Metabolism of Mother and Child Just Before and Just After Birth, *THE ARCHIVES INT. MED.*, 1911, vii, 184.



TABLE 3.—SUMMARY OF RESULTS. AVERAGES OF TRIALS

Subject	Date	Weight at Start, Kg.	Square Meters per Body Surface (M <sup>2</sup> )	Calories per Sq. M. per Hour (M <sub>0</sub> )	Variation from Average Normal Basal 30.7	Per Cent. Rise above Subject's Own Basal Metabolism	Total Calories Measured in Each Experiment		Method of Experiment	Character of Experiment
							Method of Indirect Calorimetry Rectal, Urinary, Rectal, Temp.	Method of Direct Surface Temperature		
G. L.	3-11-13	78.47	2.226	34.84	± 0	..	157.40	161.75	.....	Two basal hours.
	3-11-13	78.42	2.226	38.67	..	11	361.54	273.63	.....	First three hours after 115 Comm. glucose = 100 C. P. dextrose
	3-13-13	79.6	2.162	35.91	± 3	..	155.27	149.79	.....	Two basal hours.
F. P. D. B.	3-13-13	79.6	2.162	33.51	.....	7	333.02	341.22	.....	First three hours after 115 Comm. glucose = 100 C. P. dextrose
	3-17-13	75.31	2.200	33.99	± 4	..	219.70	214.31	.....	Three basal hours.
	3-20-13	76.00	2.211	36.82	.....	11	407.11	401.06	.....	1½ to 3½ hours after 250 Comm. glucose = 300 C. P. dextrose.
F. C. G.	3-20-13	74.24	2.177	31.08	± 2	..	222.50	227.34	.....	Three basal hours.
	4-1-13	74.42	2.188	38.09	.....	12	416.75	419.13	.....	1½ to 6½ hours after protein meal (10.5 gm. N).
	3-7-13	74.75	2.185	36.32	.....	10	317.41	307.97	.....	1 to 5 hours after 300 C. P. dextrose.
	3-17-13	75.19	2.190	36.87	.....	9	392.74	389.94	.....	1 to 6 hours after 300 C. P. dextrose taken 3½ hours after breakfast
	3-18-13	73.70	2.164	32.97	± 5	..	142.67	137.37	.....	Two basal hours.
R. H. H.	3-17-13	56.3	1.813	31.54	± 9	..	.....	.....	.....	Three basal hours.
	3-17-13	56.3	1.813	31.60	.....	10	.....	.....	.....	1 to 4 hours after breakfast of protein 13.1, fat 10.2, carbohydrate 55.5
	4-1-13	54.89	1.778	34.15	± 2	..	146.32	126.33	.....	Five hours basal.
Louis M.	3-10-13	62.00	1.929	37.62	± 9	..	116.32	129.32	.....	Two hours basal.
	3-16-13	51.70	1.709	39.66	± 6	..	116.32	129.32	.....	Six hours basal.
John L.	3-28-13	53.49	1.748	41.61	.....	22	375.89	388.22	.....	2 to 8 hours after 755 gm. beef = 22.03 N and 100 fat
L. C. M.	3-30-14	70.91	2.110	39.90	11	..	467.83	471.53	.....	Three hours basal.
	3-1-14	69.50	1.887	35.14	± 1	..	195.60	183.30	.....	Two hours basal.
	3-6-14	60.98	1.908	40.83	.....	16	131.91	140.43	.....	1 to 4 hours after 300 gm. C. P. dextrose.
							233.71	221.93	.....	
							4577.37	4569.40		

Calories, grams described on account of leaks.

The first is the standard method of Zuntz and his associates, based on the liters of oxygen consumed, which are multiplied by a factor that increases about 8 per cent. as the quotient rises from 0.72 to 0.97. The second method is based on the liters of  $\text{CO}_2$  produced, the figure for which is multiplied by a factor which decreases 24 per cent. as the

TABLE 4.—HEAT PRODUCTION OF NORMAL MEN, AGES 20 TO 50. COMPARISON OF CALORIES PER KILOGRAM AND PER SQUARE METER

Subject	Weight, Kg.	Calories per Kilogram per Hour	Calories per Sq. Meter per Hour	Percentage Variation from Average		Calories per Sq. Meter per Hour According to New Surface Area Formula	Per Cent. Variation from Average
				Calories per Kg.	Calories per Sq. Meter		
F. G. B.*	83.0	1.01	35.8	- 4	+ 5	....	...
G. L. ....	78.4	1.00	34.8	- 5	+ 2	40.7	+2
F. A. R.*	74.8	0.95	32.4	- 9	- 5	....	...
E. F. D. B. ....	74.3	1.00	34.1	- 5	0	39.8	-0
John L. ....	70.9	0.92	30.9	-12	-10	....	...
J. J. C.*	67.6	0.96	31.7	- 8	- 7	....	...
J. R.*	66.0	1.00	32.8	- 5	- 4	....	...
R. H. H. ....	62.0	1.18	37.9	+14	+11	40.9	+3
L. C. M. ....	59.5	1.11	35.1	+ 6	+ 3	40.5	+2
F. C. G. ....	54.8	1.10	34.2	+ 5	0	37.7	-5
Louis M. ....	51.7	1.21	36.7	+16	+ 7	....	...
T. M. C.*	49.0	1.13	33.8	+ 8	- 1	....	...
Average ....	....	1.05	34.2	$\pm$ 8.1	$\pm$ 4.6	39.9	$\pm$ 2.4
79 normal men in groups†							
8 weights....	75-85	1.01	35.2	- 7	+ 2	....	...
20 weights....	65-75	1.02	34.1	- 6	- 2	....	...
41 weights....	55-65	1.00	34.7	+ 1	0	....	...
10 weights....	45-55	1.18	35.5	+ 9	+ 2	....	...
Average ....	....	1.08	34.7	$\pm$ 5.8	$\pm$ 1.5	....	...

\* Determinations made by Benedict and Joslin.<sup>20</sup>

† Taken largely from work of Benedict, Emmes, Roth and Smith.<sup>10</sup>

quotient rises from 0.72 to 0.97. Tables for this latter calculation are given by Benedict and Talbot,<sup>21</sup> who prefer this method in using an apparatus in which they consider that for short periods the determination of the carbon dioxide is more exact than the determination of

21. Benedict and Talbot: Studies in the Respiratory Exchange of Infants, *Am. Jour. Dis. Child.*, 1914, viii, 1; The Gaseous Metabolism of Infants, Carnegie Institution of Washington, Pub. 201.

oxygen. It is true that in the closed circuit type of apparatus the measurement of the oxygen is subject to many corrections for changes in the barometer, temperature, moisture, etc., and that it is liable to a plus error in the case of leaks. This error affects the quotient and produces such a change in the  $\text{CO}_2$  factor that one usually obtains better results by basing the calculations on the oxygen. This is brought out clearly in Table 5, which gives a comparison of the methods of calculating the heat production from the oxygen and from the  $\text{CO}_2$ , showing the errors in the results arising from various assumed errors in the measurements. It will be noted that in the great majority of the cases

TABLE 5.—COMPARISON OF METHODS OF CALCULATION WITH ASSUMED ERRORS IN MEASUREMENT OF  $\text{CO}_2$  AND  $\text{O}_2$

CO <sub>2</sub>		O <sub>2</sub>		R.Q.	Calorific Value 1 Liter of CO <sub>2</sub>		Calorific Value 1 Liter of O <sub>2</sub>		Indirect Calorimetry Based on CO <sub>2</sub>		Indirect Calorimetry Based on O <sub>2</sub>	
Liters	Assumed Error %	Liters	Assumed Error %		Cal.	Per Cent. Change	Cal.	Per Cent. Change	Cal.	Per Cent. Error	Cal.	Per Cent. Error
12.94	0	15.64	0	0.83	5.829	.....	4.807	.....	75.40	.....	75.17	.....
12.94	0	17.20	+10	0.75	6.319	+8.4	4.708	-2.1	81.74	+8.4	80.98	+7.7
14.23	+10	15.64	0	0.91	5.424	-7.0	4.904	+2.0	77.18	+2.4	76.70	+2.0
12.94	0	16.42	+5	0.79	6.062	+4.0	4.758	-1.1	78.44	+4.0	78.13	+3.9
13.59	+5	15.64	0	0.87	5.617	-3.6	4.855	+1.0	76.33	+1.2	75.93	+1.0
12.29	-5	16.42	+5	0.75	6.219	+8.4	4.708	-2.1	77.66	+3.0	77.31	+2.8
13.59	+5	14.86	-5	0.91	5.424	-7.0	4.964	+2.0	73.71	-2.2	72.87	-3.1
12.94	0	14.86	-5	0.87	5.617	-2.7	4.855	+1.0	72.68	-3.6	72.15	-4.0

cited the error from the use of the oxygen factor is smaller than that from the  $\text{CO}_2$ . Even with a plus error of 5 to 10 per cent. in the oxygen and no error in the  $\text{CO}_2$ , the results obtained by using the oxygen are the better, since the minus change in this factor compensates for part of the error. In the two instances shown, in which the results obtained by the use of the  $\text{CO}_2$  factor are closer to the theory than those obtained by the use of the oxygen factor, it will be noted that there is a minus error in the oxygen. This is the least frequent of all the errors.

Many investigators in seeking for an index of the heat production express the results in grams or cubic centimeters of  $\text{CO}_2$ , and compare the elimination of this gas in different individuals, apparently with the impression that they are comparing the actual total metabolism. As we have seen above, a man eliminating, say, 3.13 c.c.  $\text{CO}_2$  per kg. per min-

ute might have a heat production 24 per cent. higher than another man eliminating the same amount of  $\text{CO}_2$  whose respiratory quotient was at the other end of the scale. If one uses the oxygen consumption the possible error from this source is diminished to 8 per cent. Since it is such an easy calculation to determine the actual calories by using the oxygen figure and the respiratory quotient, it seems inexcusable to leave the results at a stage which might give false impressions. It is only in special investigations on the ventilation of the lungs, etc., that the amounts of the gases themselves are of any direct interest. In most experiments it is the actual calories that need to be determined.

Experience has shown that with careful technic the indirect calorimetry in hourly periods remains fairly uniform in fasting experiments and shows regular curves in experiments after food. The direct calorimetry in hourly periods is a matter of greater technical difficulty on account of the fact that the human body is poorly constructed for accurate thermal measurements. As was shown in Paper 1, a rise or fall of 1 degree centigrade in the average temperature of the body means a storage or loss of about 58 calories if the man weighs 70 kilograms. This is based on the assumption that the specific heat of the body is 0.83, a figure which has been accepted for many decades, although without satisfactory experimental support. Rubner<sup>22</sup> has found that the specific heat of lean flesh is 0.828, of fatty tissue 0.53 and of pure fat 0.45. Rosenthal<sup>23</sup> at an earlier date had made the following determinations: compact bone 0.30, spongy bone 0.710, defibrinated blood 0.927, dried muscle 0.330. Using these figures and the figures for the average composition of the body as given by Vierort<sup>24</sup> one obtains a specific heat of approximately 0.77. A body rich in fat would, of course, approach the figure 0.45 and one rich in water would approach 1.00. Theoretically, one should change the specific heat each time a subject drinks water or voids. This latter would be a matter of small importance, but in the case of a very obese person one-half of whose weight consisted of fat, the true specific heat would not be far from 0.64.

In normal subjects the temperature changes in hourly periods are small and according to the work of Benedict and Slack,<sup>25</sup> the temper-

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22. Rubner: *Kalorimetrie*, Tigerstedt's *Handbuch der physiologische Methoden*, i, 170.

23. Rosenthal: *Ueber die spezifische Wärme thierische Gewebe*, *Arch. f. Physiol.*, 1878, p. 215.

24. Vierort: *Daten und Tabellen*. Jena, 1893, p. 249.

25. Benedict and Slack: *A Comparative Study of the Temperature Fluctuation in Different Parts of the Human Body*. Carnegie Institution of Washington, 1911, Pub. 155.

ature curves in different parts of the body are nearly parallel. Lusk<sup>26</sup> and his coworkers did not find this to be the case in the dog after the ingestion of large amounts of food since this caused a greater rise in surface than in rectal temperature. When one considers the mechanism of the regulation of body temperature in fever it becomes evident that the rise in surface temperature follows that of the internal temperature. Every clinician has felt in some patients, particularly those seriously ill, the extremities growing colder and colder while the internal temperature is rising and, conversely, has felt the surface grow warmer while the temperature is falling, demonstrating the fact that the two are not always parallel.

It was on account of these considerations that the surface thermometers described in Paper 2 were used after May, 1913, the two units of the surface thermometer being strapped over the right and left pectoralis major as near as possible to the heart and dome of the liver. They were covered with a thick layer of cotton in an effort to obtain the temperature of the subcutaneous tissue rather than that of the naked skin. After March 12, 1914, a second surface thermometer was added and its two units placed in various parts of the anterior surface of the thorax and abdomen and also in the axillae. The results have been confusing and difficult to interpret, but they have indicated clearly that the different parts of the body do not show parallel temperature curves. A fruitless search has been made for some part of the body which will give a true index of the mean temperature change. In the majority of all the experiments the rectal temperature was the more satisfactory, but in typhoid fever the surface gave better results. The method of investigation was as follows:

In a total of eighty-five experiments satisfactory rectal and surface temperature measurements were made. Twenty-eight of these experiments were on typhoid fever patients. For the reasons above stated the heat production as determined by the method of indirect calorimetry was considered to be the true heat production, and the results of the direct calorimetry as calculated by three different methods were compared with this as shown in the table below. In all three methods the figure for the heat eliminated from the body was, of course, the same. To obtain the heat produced, the heat stored in or lost from the body, as determined by each of the two measurements, and by a mean of the two, has been added to or subtracted from the heat eliminated.

It will be seen from Table 6 that in the total of 85 experiments the rectal temperature gave the best results, approximating the theoretical more closely than either of its competitors in 36 cases, coming within 5

26. Williams, Riche and Lusk: Metabolism of the Dog Following the Ingestion of Meat in Large Quantity, *Jour. Biol. Chem.*, 1912, xii, 349.

per cent. in 62 cases and involving a total error of only 0.90 per cent. While the surface temperature gave the best results in 24 cases, it showed an error of over 15 per cent. in 5 cases and did not prove as reliable as the mean of surface and rectal. In typhoid fever the honors were more evenly divided and all three methods gave surprisingly good results in spite of the large changes in body temperature sometimes encountered. The surface temperature alone gave the best results in 13 of the 28 experiments and also the lowest total error.

TABLE 6.—COMPARISON OF SURFACE AND RECTAL TEMPERATURES AS AN INDEX OF AVERAGE BODY TEMPERATURE; PERCENTAGE DIFFERENCES BETWEEN INDIRECT CALORIMETRY AND DIRECT CALORIMETRY CALCULATED ACCORDING TO THREE METHODS

Percentage Difference in Individual Experiments	Number of Experiments Falling in Each Group					
	Twenty-Eight Typhoid Experiments			Eighty-Five Experiments in Various Diseases, Including the Twenty-Eight Typhoid Observations		
	Rectal Temperature Alone	Surface Temperature Alone	One-half Rectal, One-half Surface	Rectal Temperature Alone	Surface Temperature Alone	One-half Rectal, One-half Surface
0 to 5.....	18	18	18	62	41	53
5 to 10.....	9	9	10	19	28	27
10 to 15.....	1	1	0	4	11	4
15+.....	0	0	0	0	5	1
Total difference.....	-1.32	-1.17	-1.24	-0.90	-1.46	-1.18
Number giving results nearest to indirect.....	8	13	7	46	24	15

As a result of the above analysis the rectal temperature has been adopted as the standard indicator of the average body change in hourly periods, but with a full realization of its limitations. In many experiments, particularly in those with rapidly changing temperature, better results would be obtained by using the surface temperature, but surface thermometers are more easily displaced than rectal and are not so reliable in the long run. Theoretically, one would obtain the best results by the use of many thermometers placed in the rectum, axillae, groin, on the surface of the body in many areas, giving each measurement an estimated weight, and then calculating the mean temperature change. Our attempt to do this in a small way by giving the rectal and surface equal weights did not lead to better results. For many reasons it seems advisable to attach as little apparatus as possible to the subject, and it is



doubtful if the use of many thermometers at one time will ever become a standard method.

There may be several reasons why these results are not in accord with the conclusion of Benedict and Slack. Working with normal subjects who showed comparatively small fluctuations in body temperature, they made many measurements at different depths in the rectum and vagina and found that while there was a sharp fall in temperature between a point 7 cm. within the rectum and a point just within the anus, nevertheless the temperature of points at different depths remained parallel, though at a different level. Temperatures taken in the well-closed axilla and groin were also parallel with the rectal. The mouth was found to be an unsatisfactory place to obtain the mean body temperature. Considerable difficulty was experienced in obtaining satisfactory measurements of the surface of the body and of the hands, and the writers speak of the difficulty of devising a thermometer that will be shielded so that it may assume the body temperature and yet not interfere with the natural liberation of heat.

As we have mentioned above, our surface thermometers were covered with a thick layer of cotton wool and represented a subcutaneous rather than a surface measurement, and therefore not comparable to the axillary, groin and shallow rectal measurements of Benedict and Slack. All of the latter are in the neighborhood of large blood-vessels and might be expected to rise and fall simultaneously.

All of this brings us back to the desirability of using the method of indirect calorimetry as the standard and checking its accuracy by the level of the respiratory quotient and the agreement with the direct calorimetry. All the evidence of this laboratory shows that the quotient rises and falls in regular curves in rest experiments when hourly periods are used. If, therefore, in any experiment the quotient shows a variation not accounted for by recent food, we suspect an error and usually find it compensated for in the next period. This error is almost always found in the calculation of the residual oxygen in the box at the close of the hour. Luckily there is an automatic correction in the method of calculating the indirect calorimetry. If in the first hour the oxygen estimation be too high, the quotient will be too low, and consequently the factor by which the oxygen is multiplied will be diminished. In the second hour when the error has been compensated for, the oxygen estimation will be too low, the quotient too high and the factor increased. This is another reason why the indirect calorimetry is more reliable than the oxygen consumption as an index of metabolism.

The method of direct calorimetry serves as an invaluable check, and if in any two- or three-hour experiment during which the body

temperature changes less than half a degree, the methods of indirect and direct calorimetry do not agree within 5 per cent., one should suspect a defect in the calorimeter. If in the next experiment a similar divergence be found, an alcohol check should be made and the error located. If one can prove that the error was due to any one particular determination, all calculations affected by this must be rejected as in the two experiments on F. C. G. It is by no means necessary to reject the results of the method of calorimetry not affected by the error. There is only one determination that enters into both methods of calculation, but an error in this would cause the two methods to diverge and not to err in the same direction. If through gross carelessness the first sulphuric acid bottle were allowed to gain so much weight that water vapor passed by into the  $\text{CO}_2$  absorber, the direct calorimetry would be too low and the indirect too high, since both the quotient and the oxygen factor would be increased.

#### DETERMINATION OF THE AVERAGE NORMAL.

The selection of the proper normal base line is a matter of extreme difficulty. It is also a matter of prime importance in determining whether or not a patient or group of patients shows a total metabolism which is above or below the normal limits. In dealing with patients suffering from acute diseases it is sometimes possible to wait until the patient recovers completely and then determine his normal heat production. This is not always practicable and even when it can be done one has no guarantee that the metabolism has returned to normal unless several measurements at considerable intervals be made. In the case of patients with chronic diseases this method is out of the question. The method most commonly used is that of selecting groups of normal controls to correspond as nearly as possible to each individual patient. This of course is the ideal method if many controls be selected, but it is extremely doubtful if any investigator up to the present date has been able to gather enough satisfactory controls for each patient. The recent work of Benedict, Emmes, Roth and Smith<sup>10</sup> may remedy this, on account of the large number of individuals whose metabolism was determined. Even with this wealth of material one may err if allowed to pick out a small group. The individual variation is large, as one can see from a careful study of the figures. It is, perhaps, unfair to draw many deductions before the full description of the subjects is published, but we may rely on the statement that all were in presumably good health. The average heat production of the 89 men was 833 calories per square meter per day or 34.7 calories per square meter per hour. The average heat production of the 12 men studied in the bed calorimeters and grouped in Table 4 was 34.2 calories

per square meter per hour. This striking agreement is another proof that the Benedict universal respiration apparatus gives results which are almost identical with the calorimeter. For this reason the 7 subjects examined by us have for purposes of calculation been grouped with the 89 of Benedict, Emmes, Roth and Smith. In order to rule out those who were distinctly over- or underweight, the subjects were all plotted in a curve, the height forming the abscissa and the weight the ordinates. All but 9 of the subjects could be grouped between two lines not very far apart. Of the 9, W. S., O. F. M., Prof. C., H. F., F. E. M. and F. A. R. were evidently much heavier in proportion to their height than their fellows, and for this reason excluded from the averages. It is interesting to note that their average heat production was 31.5 calories per square meter. Two of the 9, R. A. C. and B. N. C., were evidently very light in proportion to their height. E. P. C. came just outside the line, but so close to it that he has not been excluded from the averages. All those over 50 years of age were arbitrarily excluded and also those under 20 years. To the remaining 72 were added the normal controls of the present paper. This process of exclusion and addition left a fairly homogeneous total of 79 whose average metabolism was 34.7 calories per square meter per hour, or exactly the same as that of the original 89 before the addition of 7 and the exclusion of 17. These 79 have been divided into four groups according to body weight in Table 4.

If we plot the heat production of all the subjects according to surface area, the range of individual variation becomes apparent. Of the total 79 we find 40 within 5 per cent. of the base line drawn at the average figure 34.7, 28 are from 5 to 10 per cent. from the average and 11 are more than 10 per cent. from the average. Of these, 6 were between 10 and 14 per cent. above, and 5 were between 10 and 15 per cent. below. This means that when we speak of a normal average we must remember a normal variation of at least 10 per cent. above and below and realize that in about 14 per cent. of the normal men the variation may be plus or minus 10 to 15 per cent. One cannot help but feel that most of the cases showing a variation of more than 10 per cent. from the average will be found to present some distinct cause for the unusual metabolism, such as an unusual degree of muscular development or muscular disuse or an unsuspected disturbance of the thyroid secretion, or the mild infection with tuberculosis which all of us pass through at some time in our lives. At any rate, one can be fairly certain that if the total heat production be 15 per cent. from the average it is distinctly abnormal, and if it be more than 10 per cent. from the average it must be regarded with great suspicion.

It may be argued that some of the variation may be due to differences in body weight. If we study the 24 normal subjects in the table we have been considering, whose weights are between 60 and 65 kg., the same variation is apparent. Of the 24, only 13 are within 5 per cent. of the average, 5 are between 5 and 12 per cent. above and 6 are from 5 to 10 per cent. below. If one investigator chanced to select this last group of 6 for his controls his average would be about 15 per cent. lower than if he selected the group of 5 cases with high metabolism. This of course is an extreme instance. It may still be argued that the factor of height must be considered. In the same table we find an exceedingly homogeneous group of 7 men whose weights are between 60.1 and 60.5 kg. and whose heights are between 171 and 175 cm. Even in this group there is a difference of 13 per cent. between the highest and the lowest and a difference of 9 per cent. between the averages of the highest 4 and the lowest 3 in this group.

This somewhat lengthy discussion is intended to show the chances of serious error in selecting any small group of normal controls to compare with a pathological case. One cannot say just how large the group should be, but it is safe to say that it must exceed 5, should exceed 10 and if possible, 50. It is obviously much better to use all the normal controls so far studied and let personal selection play no part. This can be done by basing all comparisons on the average heat production per square meter of body surface.

In Table 4 we find a comparison of the heat production calculated according to surface area and according to weight. A study of the percentage variation from the average shows clearly that all four weight groups are within 2 per cent. of the mean heat production per square meter of body surface. In other words, one can determine the average normal by this method by using a group of individuals of any weight within ordinary limits. On the other hand, the figures per kilogram of body weight show the customary diminution as weight increases and there is a difference of 16 per cent. between the heavy group and the light group. In other words, there is no such thing as an average calories per kilogram for normal men, but only a normal average for each weight. To find the normal for a given man by this method one must consult a curve. To find the normal for a given man by the method of surface area one needs only to remember the figure 34.7.

Shortly after the experimental work on the normal controls was completed it seemed advisable to investigate the accuracy of Meeh's formula and if possible devise a new formula which could be applied to individuals who depart materially from the average body form. Five subjects were measured and it was found that there was a con-

sistent plus error in Meeh's formula which, in the case of a very fat woman, amounted to 36 per cent. In two of the normal controls whose heat production had been determined, the surface area was actually measured and the errors in Meeh's formula were found to be as follows: E. F. D. B., + 14 per cent., R. H. H., + 7 per cent. In three others, G. L., F. C. G. and L. C. M., the surface area was calculated by the new formula and found to be, respectively, 14.5 per cent., 9.3 per cent. and 13.4 per cent. lower than the results obtained by Meeh's formula. Since in all four cases the new surface area figures are lower than the old results obtained from Meeh's formula, the heat production per square meter of body surface, according to the new formula, would be about 7 to 15 per cent. higher, the average being 39.9. As will be seen in the last two columns of Table 3, the new results are somewhat more uniform than the old results, but are on a higher level, and it is quite possible that it may be necessary to adopt a higher normal average than 34.7. The general principle of Meeh's formula seems to be correct for individuals of average shape, and for this reason it may be used as the standard in large groups of subjects. In the case of very fat individuals, Meeh's formula would give a figure for the calories per square meter which would be much too low. It seems probable that some of the variations from the average normal figure per square meter can be explained by the variable error in the old formula. Future use of the new formula will, it is hoped, clear up this point. The details of the new method will appear in the following paper.

There is but little evidence against Rubner's law that metabolism is proportional to surface area. As we have seen there is a plus error in Meeh's formula for determining surface area. Nevertheless, in a group of normal men of approximately average build between the weights of 45 and 85 kilograms the metabolism is, on the whole, proportional to the surface area as determined by Meeh's formula. When we come to extend Rubner's law to babies and dogs studied in the modern types of apparatus with the modern scrupulous care to exclude the effect of muscular work, we find the figure for the calories per square meter changed, yet not nearly so much changed as the figure for the calories per kilogram of body weight. Murlin and Hoobler<sup>27</sup> have demonstrated that in a group of infants between the ages of 2 and 12 months the metabolism is proportional to weight rather than to surface area, and have pointed out the effect of age, showing that among infants of the same age the metabolism is proportional to the

27. Murlin and Hoobler: The Energy Requirement of Normal and Marasmic Children with Special Reference to the Specific Gravity of the Child's Body, *Proc. Soc. Exper. Biol. and Med.*, 1914, xi, 115.

surface area. Benedict and Talbot<sup>28</sup> believe that the metabolism of infants is not proportional to surface area, but is proportional to protoplasmic mass. Table 7 shows that comparing babies and dogs with adults the method of surface area gives results much closer to the average for men than the method of comparison by weight. It may seem superfluous at this late date to argue at length in support of Rubner's law of surface area, but this law is becoming the center of an active discussion.

The percentage of calories derived from protein in the fasting experiments is a matter of some interest in the discussion of the subject of the toxic destruction of protein. The average figures for the basal experiments on the various subjects are as follows: G. L., 16.5 per cent.; E. F. D. B., 19 per cent.; F. C. G., 18 per cent.; Louis M., 22 per cent.; John L., 15 per cent.; L. C. M., 21.5 per cent. To this list may be added the figures for several normal controls from the work of Benedict and Joslin:<sup>29</sup> F. G. B., 17.6 per cent.; J. R., 15.6 per cent.; J. J. C., 15.7 per cent.; D. B., 21.6 per cent.; H. F. T., 19.9 per cent.; Dr. S., 15.5 per cent.; V. G., 12.7 per cent.; T. M. C., 14.8 per cent. These figures represent largely the effect of the amount of protein in the diet of the preceding day. They are by no means the figures that would be obtained had the subjects been maintained on a protein minimum for a few days before the experiments.

#### THE EFFECTS OF FOOD

The experiments on the effects of food were intended primarily as controls on the effects of similar meals given to patients with typhoid fever and exophthalmic goiter. While the subject of the specific dynamic action of food is one of great interest and importance it was felt that the chief function of the calorimeter in Bellevue Hospital was the investigation of pathological conditions. Consequently, very simple protein and carbohydrate meals which could be given in typhoid fever were the only ones studied, and the study of the effects of fat was postponed. During the season of 1913 commercial glucose containing dextrose 42.37 per cent., dextrin 44.57 per cent. and water 13.50 per cent. was used. This is one of the cheapest of food-stuffs, is readily soluble in water, is not very sweet and on account of its chemical composition should be rapidly absorbed. It has been found of great service

28. Benedict and Talbot: Studies in Respiratory Exchange of Infants, *Am. Jour. Dis. Child.*, 1914, viii, 1; Gaseous Metabolism of Infants, Carnegie Institution of Washington, 1914, Pub. 201.

29. Benedict and Joslin: A Study of Metabolism in Severe Diabetes, Carnegie Institution of Washington, 1912, Pub. 176, p. 103.



in feeding many of the patients and in some ways is preferable to the less soluble lactose. In the season of 1914 chemically pure dextrose was used in order to compare its effects with that of the mixture. The chief protein meal used in typhoid consisted chiefly of casein in the form of cottage cheese and fat-free milk with the whites of two or three eggs and some egg yolk. It did not make a very palatable mixture, but it was consumed by most of the typhoid patients without much complaint and it certainly did them no harm. While it might have been more satisfactory to give meat, it did not seem justifiable until we had more experience with its effects in fever.

TABLE 7.—COMPARISON OF CALORIES PER KG. AND PER SQUARE METERS OF BODY SURFACE

Investigator	Subject	Calories per Kg.	Calories per Sq. M.	Per Cent. Variation from Average for Men	
				Accord- ing to Calories per Kg.	Accord- ing to Calories per Sq. M.
Benedict and collaborators	79 men	1.08	34.7		
Lusk	Dog 1	1.65	31.6	-36	-9
Lusk	Dog 2	1.75	32.7	-60	-6
Lusk	Dog 3	1.45	29.8	-73	-14
Lusk and McCrudden	Dwarf, Wt. 21.3 kg.	1.21	32.3	-17	-7
Howland	Baby 1	2.89	39.5	-168	-14
Howland	Baby 2	3.45	45.7	+220	+31
Murlin and Hoobler	Average 6 infants	2.69	36.3	+150	+5
Benedict and Talbot	Average 10 normal in- under 1 month	1.95	25.6	+81	-26
	Average 11 normal in- fants between 1 and 10 months	2.21	35.5	+105	+2

Two different methods were used in obtaining a base line to represent the metabolism without food. At first the fasting metabolism was determined in the early morning and the food given while the subject was in the calorimeter. This necessitated a sojourn of three or four hours in the box after the food in addition to the two hours before the food. Even normal individuals become tired after three hours of absolute quiet in a calorimeter and it was evident that patients would be restless in such long experiments. Another disturbing factor was the gradual change in the metabolism with the different hours of the day. The method finally adopted has given great satisfaction. It is the method used so successfully by Lusk<sup>3</sup> on the dog. The basal metabolism is determined in a two- or three-hour experiment and two

days later the food is given before the subject is sealed in the box and the metabolism determined during the same hours studied in the fasting experiment. The basal metabolism in our experience does not change rapidly enough to make this method inaccurate. The high metabolism in the first experiment on E. F. D. B. was due to restlessness, and the low metabolism in the first experiment on F. C. G. was due to profound sleep. Between May 17, 1913, and May 18, 1914, the heat production of E. F. D. B. did not vary 3 per cent. in the three

TABLE 8.—INCREASE IN HEAT PRODUCTION FOLLOWING INGESTION OF DEXTROSE

Subject	Hours After Glucose	Per Cent. Rise	Extra Calories	Extra Calories from Combustion of Carbohydrate	Specific Dynamic Action, Per Cent.
G. L.: 100 glucose.....	0-1	20	15.52	.....	..
	1-2	10	8.16	.....	..
	2-3	3	2.26	.....	..
E. F. D. B.: 100 glucose.....	0-1	3	2.63	24.56	11
	1-2	11	8.78	22.38	39
	2-3	9	6.77	20.41	39
	3-4	6	4.28	22.96	18
Total .....	...	..	22.46	91.31	Av. 25
E. F. D. B.: 200 glucose.....	1-2	13	9.18	41.68	22
	2-3	17	11.73	37.83	31
	3-4	8	5.98	39.22	15
	4-5	7	5.12	40.08	13
Total .....	...	..	32.01	158.81	Av. 20
L. C. M.: 200 glucose.....	1-2	24	15.09	33.37	45
	2-3	16	10.49	41.04	26
	3-4	16	10.25	40.85	25
Total .....	...	..	35.83	115.26	Av. 31

tests made. In some of the ward patients studied the metabolism has remained constant from day to day and even in typhoid fever has changed in gradual curves. Two hundred grams of dextrose or its equivalent caused an average increase of 12.5 per cent. in the first three to six hours after its ingestion. One hundred grams caused an average increase of 9 per cent. The casein meal with 10.5 gm. N increased the metabolism 12 per cent., the beef with almost 24 gm. nitrogen increased

it 22 per cent.\* A more detailed study of the effects of food is given in Tables 8 and 9, which show the effects in the different periods. The percentage increase in metabolism and the extra calories produced are calculated from the nearest basal determination. The extra protein calories produced are calculated from the increase in the urine nitrogen above the average hourly elimination of the nearest basal determination. The extra grams of urinary nitrogen when multiplied by the factor 26.51 give the extra calories from the combustion of protein during that hour. The extra calories produced when divided by this

TABLE 9.—INCREASE IN HEAT PRODUCTION FOLLOWING PROTEIN MEAL

Time After Protein Meal, Hours	Per Cent. Rise in Metabolism	Extra Calories Produced	Extra Protein Calories Metabolized. Extra Urine N $\times$ 26.51	Specific Dynamic Action, Per Cent.
F. F. D. B.: 10.5 N				
1½ to 2½ .....	8.0	5.93	8.96	100
2½ to 3½ .....	16.5	12.34	8.27	140
3½ to 4½ .....	12.1	9.03	10.13	90
4½ to 5½ .....	15.5	11.54	1.56	708
5½ to 6½ .....	6.8	5.04	1.56	300
Total .....	....	43.88	30.48	Av. 144
Louis M.: After 23.93 N				
2 to 3 .....	15.1	9.68	4.80	200
3 to 4 .....	16.2	10.36	4.59	205
4 to 5 .....	28.0	17.94	11.88	150
5 to 6 .....	27.5	17.62	13.04	135
6 to 7 .....	17.6	11.30	16.33	69
7 to 8 .....	25.7	16.45	15.64	106
Total .....	....	83.35	66.28	Av. 126

figure for the extra protein calories metabolized, give the specific dynamic action in the sense of Rubner (see Note 2, Williams, Riche and Lusk, p. 370), amounting to as much as 144 per cent. and 126 per cent. for the two experiments. The accuracy of this method of calculation may be impaired by the lag in the excretion of nitrogen by

\* Since the completion of this paper two more normal men have been given the test meals. Morris S. on Dec. 18, 1914, showed a rise of 6.5 per cent. after a meal containing 9.6 gm. nitrogen. Albert G. on Jan. 6, 1915, showed an increase of 9 per cent. in his metabolism after 115 gm. commercial glucose (100 gm. dry glucose)

the kidneys. In the dextrose experiments the method of calculation is slightly different from the method used by Lusk.<sup>2</sup> The extra calories produced by the combustion of carbohydrate are reckoned as follows: In the nearest basal determination the average figure for the calories per hour is multiplied by the percentage of calories furnished by the combustion of carbohydrate. A similar calculation is made in each hour of the experiment in which dextrose was administered and the extra carbohydrate calories metabolized in each hour determined. This figure divided into the extra calories produced gives the specific dynamic action of 25, 20 and 31 per cent. in the three experiments.

#### SUMMARY AND CONCLUSIONS

Seven normal men were studied with and without food as controls for the observations on patients in the metabolism ward. Their average basal metabolism (at perfect rest, fourteen to eighteen hours after their last meal) was 34.8 calories per hour per square meter of body surface. The average basal metabolism of 89 normal men studied by Benedict, Emmes, Roth and Smith<sup>10</sup> was 34.7 calories. The average of the 7 men studied in the Sage bed calorimeter in Bellevue and of the 5 men studied in Benedict's bed calorimeter in Boston was 34.2 calories. As a result we have adopted the figure of 34.7 calories per square meter of the body surface as the average heat production of normal men between the ages of 20 and 50 years.

All of the subjects studied in the bed calorimeter were within 11 per cent. of this average. Of the 79 men of normal figure between the ages of 20 and 50 studied by Benedict and collaborators, 86 per cent. were within 10 per cent. of the average and the remainder between 11 and 15 per cent. If, therefore, the heat production of a given subject suffering from some pathological condition is more than 10 per cent. above or below the average it may be regarded as abnormal, but cannot be proved abnormal unless the departure from the average is at least 15 per cent.

Groups of men of weights between 45 and 85 kilograms show a mean heat production within 2 per cent. of the average according to surface area. According to calories per kilogram of body weight the group weighing between 75 and 85 kg. produces 7 per cent. less than the average figure and the group between 45 and 55 kg. produces 9 per cent. more than the average. The conclusion is therefore drawn that among groups of men of varying weights metabolism is proportional to surface area according to Rubner's law and is not proportional to body weight. By using the surface area as a basis one can refer all individuals to a single average normal figure, 34.7. If one uses the body weight as a basis a different normal figure is required for each weight.

The methods of direct and indirect calorimetry in disease agree in two- and three-hour periods; and in health may be found to agree in hourly periods. In the total measurement of 4,577 calories in the experiments reported in this paper the two methods have agreed within 0.17 per cent. In a total of thirty one-hour periods on one normal subject the two methods have agreed within 5 per cent. in twenty-one individual hours and within 10 per cent. in twenty-seven of the periods.

The method of indirect calorimetry using the oxygen consumption as a basis gives the best results in hourly periods. The method of direct calorimetry in short periods is made difficult by uncertainty as to the correct specific heat of the body and also by the fact that the different parts of the body do not always change their temperatures at the same rate. On the average one obtains the best results by considering that the rectal temperature change indicates the mean temperature change of the body, but in typhoid fever the surface thermometers often give a better indication of the mean body change.

The most satisfactory method of determining the effect of food in increasing heat production in normal subjects and patients is to determine the basal metabolism at frequent intervals, and on days shortly after a basal determination administer the food before the subject is sealed in the calorimeter. It has been found that 200 gm. of dextrose or its equivalent in commercial glucose or a casein meal with 10.5 gm. of nitrogen increase the heat production by about 12 per cent. over a period of three to six hours. The basal metabolism of patients with various diseases and the effects of this same food will be discussed in subsequent publications.

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## CLINICAL CALORIMETRY

### FIFTH PAPER

#### THE MEASUREMENT OF THE SURFACE AREA OF MAN \*

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NEW YORK

Recent work on the basal metabolism of infants and adults has revived interest in Rubner's law that heat production in different individuals and species of animals is proportional to the surface area. This law was first definitely formulated by Rubner<sup>1</sup> in 1883, although suggested by Bergman<sup>2</sup> many years before. At the time the experimental work in support of this theory was done no record was kept of body movements and men and animals were allowed to move during the periods of investigation. The average heat production per square meter of body surface was about 1,000 calories per day. In modern work, where the influence of muscular activity is absolutely excluded, the figure is in the neighborhood of 830 calories per square meter per day, as has been shown in Paper 4 of this series. With these new figures it is not unnatural that many investigators have felt that the whole question must be studied anew. Very recently Murlin and Hoobler<sup>3</sup> in New York and Benedict and Talbot<sup>4</sup> in Boston have all concluded that among infants metabolism is more nearly proportional to body weight than to surface area. If this is true for adults, it is a matter of great theoretical and practical importance.

It is obvious that the whole question rests on the accuracy of the determinations of the basal metabolism and of the surface area. The methods of determining the metabolism have been greatly improved, leaving the surface area the doubtful factor. The number of formulas for surface area determination is large, the number of individuals

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\* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division of Bellevue Hospital.

1. Rubner: Ueber den Einfluss der Körpergrösse auf Stoff- und Kraftwechsel, *Ztschr. f. Biol.*, 1883, xix, 545.

2. Bergman: *Wärmeökonomie der Thiere*, Göttingen, 1848, p. 9.

3. Murlin and Hoobler: The Energy Metabolism of Normal and Marasmic Children with Special Reference to the Specific Gravity of the Child's Body, *Proc. Soc. Exper. Biol. and Med.*, 1914, xi, 115.

4. Benedict and Talbot: Studies in the Respiratory Exchange of Infants, *Am. Jour. Dis. Child.*, 1914, viii, 1; The Gaseous Metabolism of Infants, *Carnegie Institution of Washington*, 1914, Pub. 201.



whose area has been measured is small. In 1879 Meeh<sup>5</sup> finished his painstaking and time-consuming work which has remained the standard ever since. He measured six adults and ten children, using a variety of methods. Some parts of the body were marked out in geometrical patterns, which were then traced on transparent paper. The areas of these were then determined by geometry, or, if the pieces of paper were very irregular, by weighing. Some of the cylindrical parts of the body were wound with strips of millimeter paper like a bandage. Funke<sup>6</sup> in one case covered the skin of a cadaver with adhesive material and pasted over this squares of paper. Fubini and Ronchi<sup>7</sup> measured one man by marking out the anatomical regions of the body and determining the areas geometrically. Bouchard<sup>8</sup> used this same method in measuring a number of adults. He speaks of a plan of clothing the body in tights made of some thin, flexible, inelastic sort of paper, the area of which could be determined by weighing. Apparently, he was not able to find the right material. He mentions the fact that M. Bergonie measured surface area by means of plates of lead, and that M. Roussy used a very ingenious cylinder with a revolution counter which he passed over the whole surface of the body. Bouchard also states that D'Arsonval determined the surface area electrically by clothing the man in silk tights and charging him as one would charge a Leyden jar, calculating the surface by applying a metal plate of known area. Lissauer<sup>9</sup> measured twelve dead babies by covering the skin with colored adhesive material and then applying silk paper and measuring the area of the paper geometrically or with a planimeter.

Meeh<sup>5</sup> as a result of his own measurements, based his formula for determining surface area on the fundamental mathematical law that the surfaces of similar solids are proportional to the  $\frac{2}{3}$  power of their volumes. Using the body weight to represent volume he determined that the constant 12.312 when multiplied by the cube root of the square of the weight in kilograms gave results which came within 7 per cent. of all his measurements of adults and older children. The constant for infants was 11.9 and for various species of animals still different. Miwa and Stöltzner<sup>10</sup> felt the need of introducing linear measurements

5. Meeh: Oberflächenmessungen des menschlichen Körpers, *Ztschr. f. Biol.* 1879, xv, 425.

6. Funke: Moleschott's Untersuchungen, *z. Naturlehre*, 1858, iv, 36.

7. Fubini and Ronchi: Ueber die Perspiration der CO<sub>2</sub> beim Menschen Moleschott's Untersuchungen, *z. Naturlehre*, 1881, xii.

8. Bouchard, Ch.: *Traité de Pathologie générale*, Paris, 1900, m<sup>1</sup>, 200, 384.

9. Lissauer, W.: Ueber Oberflächenmessungen an Säuglingen und ihre Bedeutung für den Nahrungsbedarf, *Jahrb. f. Kinderh.*, 1902, lviii, 392.

10. Miwa and Stöltzner: Bestimmung der Körperoberfläche des Menschen, *Ztschr. f. Biol.*, 1898, xxxvi, 314.

and chose the height (L) and the circumference of the chest (U) at the level of the nipples in men and just above the breasts in women, retaining the weight (G) as a factor. Using Meeh's measurements they determined by means of the following formula,

$$\text{Surface} = \frac{K \cdot U \cdot G \cdot L}{\sqrt{U \cdot L \cdot U^2}} \text{ using an average constant (K) of 4.5335.}$$

This formula, which might have been simplified to  $\text{Surface} = K \sqrt[3]{U^2 \cdot G \cdot L}$  has never been much used, although its originators have shown that it comes closer to Meeh's cases than Meeh's own formula. Lissauer from the measurement of babies, almost all of whom were atrophic, retained the principles of Meeh's formula, but found that the constant 10.3 gave better results than the constant 11.9. This indicated that Meeh's figure was about 16 per cent. too high. The formula of Miwa and Stöltzner, according to Lissauer, gave no better results than that of Meeh. Howland and Dana,<sup>11</sup> using the measurements of Meeh and Lissauer, have devised a simple formula in which the surface area (y) of the child equals the weight in grams (x) multiplied by a constant 0.483 (m) plus 730 (b). This is expressed in the terms  $y = mx + b$ .

Bouchard found a consistent plus error in Meeh's formula as given in Table 1.\* In his own formula, which requires twenty-five pages of tables for its application, he uses the body weight, the height and the diagonal circumference of the abdomen from the hollow of the back to a point somewhere above the umbilicus according to the degree of obesity. Bouchard states that a measuring tape passed around the abdomen and moved back and forth will of itself find the right circumference, which he calls the "tour de taille." Bouchard's formula has been very little used, as it seems to be difficult to understand and apply.

Recently Dreyer, Ray and Walker<sup>12</sup> have made many measurements of birds and small mammals and have found that the surface area, blood volume, cross sections of the aorta and trachea are all nearly proportional to the  $\frac{2}{3}$  power of the weight. The formula which applies to all these measurements is  $S = k W^n$ , in which S is the surface, blood volume, etc.; k is a constant which varies with the species; W is the weight, and n is approximately 0.70-0.72 instead of 0.666 which would be the  $\frac{2}{3}$  power. Benedict and Talbot<sup>1</sup> have suggested that the active mass of protoplasmic tissue develops normally on this ratio. They are convinced that metabolism is determined, not by the body

11. Howland and Dana: A Formula for the Determination of the Surface Area of Infants, *Am. Jour. Dis. Child.*, 1913, vi, 33.

12. Dreyer and Ray: *Phil. Trans.*, 1909-10, cci, Series B, p. 133. Dreyer, Ray and Walker: The Size of the Aorta in Warm-Blooded Animals and its Relationship to Body Weight and to Surface Area, Expressed in a Formula, *Proc. Roy. Soc.*, 1912-1913, lxxxvi, Series B, pp. 39 and 56.

surface, but by the active mass of protoplasmic tissue. If both are assumed proportional to the same thing, it will be a difficult matter to prove which is the more important factor.

As shown in Paper 4 of this series, the metabolism of the normal and pathological subjects studied in the Sage respiration calorimeter in Bellevue Hospital has been expressed in terms of calories per square

TABLE 1.—DETERMINATION OF ERROR IN MEEH'S FORMULA AS APPLIED TO MEASURED INDIVIDUALS

Subject	Observer	Weight, Kg.	Surface Area as Measured, Sq. Cm.	Constant for Meeh's Formula, Area Divided by Wt. %	Error in Meeh's Formula	Age, Yrs.	Height, Cm.	Body Form
Benny L. ....	D.B. and D.B. ....	24.2	8,473	10.13	+21	36	110.3	Cretin. Short and fat.
Hagenlocher ....	Meeh. ....	25.30	11,883	12.80	- 4	13.1	137.5	Medium strong.
Very thin woman	Bouchard. ....	31.8	12,737	12.69	- 3	...	...	Very thin.
Korner ....	Meeh. ....	35.38	14,388	13.17	- 7	15.7	152	Muscular.
Schneck ....	Meeh. ....	50.00	17,415	12.96	- 5	36	158	Very thin.
Adult man ....	Fobini and Ronchi	50.00	16,067	11.84	+ 4	...	...	?
Nagel ....	Meeh. ....	51.75	18,158	12.96	- 5	45	160	Somewhat thin.
Fr. Brotbeck ...	Meeh. ....	55.75	19,206	13.16	- 6	17.7	169	Very strong and muscular.
Naser ....	Meeh. ....	59.50	18,695	12.27	+ 0	...	170	Somewhat thin, but well proportioned.
Normal man ....	Bouchard. ....	61.6	18,930	12.13	+ 2	...	...	Normal man.
Fr. Haug ....	Meeh. ....	62.25	19,204	12.01	+ 2	26.2	162	Strong.
Morris S. ....	D.B. and D.B. ....	64.0	16,720	10.45	+17	21	164.3	Short and rather stout.
R. H. H. ....	D.B. and D.B. ....	64.08	18,375	11.49	+ 7	22	178	Tall and thin.
Forstbauer ....	Meeh. ....	65.50	20,172	12.48	- 1	66	172	Still very strong.
E. F. D. B. ....	D.B. and D.B. ....	74.05	19,000	10.55	+14	32	179.2	Tall, average build.
Normal woman...	Bouchard. ....	76.5	19,484	10.81	+14	...	...	Normal woman.
Kehr ....	Meeh. ....	78.25	22,435	12.26	+ 0	36	171	Corpulent.
Large man ....	Bouchard. ....	88.6	21,925	11.03	+12	...	...	Large strong man.
Mrs. McK ....	D.B. and D.B. ....	93.0	18,592	9.96	+36	...	149.7	Very short and very fat.
Very fat man...	Bouchard. ....	140.0	24,966	9.26	+33	...	...	Very fat man.

meter per hour. The work had progressed but a short distance when it was obvious that no formula based on weight could give the surface area of all the patients with any great degree of accuracy. Among the patients studied were men emaciated from typhoid fever and hyperthyroidism, men of normal shape and men with acromegaly, hypophysial dystrophy and cretinism. Eventually, it is hoped every conceivable shape will be studied. A formula such as Meeh's is accurate only for objects of different size, *but of similar shape*.

The obvious method for determining surface area is to multiply the length by the average width. An attempt has been made to measure a characteristic length and an average or characteristic circumference of each part of the body and determine the area of the part by multiplying the two and correcting by a constant factor. The sum of the parts will then give the total surface area of the body. When the proper measurements have been selected and the constants for each part determined, it is evident that the method can be applied to individuals of varying shape no matter what disproportion may exist between the different parts of the body.



Fig. 16.—The cretin, Benny L., with mold of his surface area.

#### INDIVIDUALS MEASURED

The five individuals whose surface area was measured differed from each other in bodily form to a marked degree. All of them had served as the subjects of observations in which the basal metabolism was determined. Benny L. was a cretin 36 years old with the general mental and physical development of a boy of 8. As his photograph (Fig. 16) shows, he was short and stocky, with prominent abdomen, short thick extremities and rather small head. Morris S., 21 years old, was measured three months after he was discharged from the hospital, where he

had been confined three and one-half months with a severe attack of typhoid fever. He had recovered even more than his usual weight in the hospital and during the subsequent stay in the country. At the time he was measured he was of well rounded figure, almost stout. He was short and of small frame, with small hands and feet. R. H. H., a chemist, 22 years old, was tall and thin, with long, slim bones, sinewy muscles and very little subcutaneous fat. E. F. D. B., 32 years old, was tall, but of average build. Mrs. McK. was a very short and very fat woman whose metabolism had been studied in great detail by Dr. David

TABLE 2.—MEASUREMENTS USED IN FORMULA

Index Letter of Part Measured	Benny L.	Morris S.	R. H. H.	E. F. D. B.	Mrs. McK.
A.....	57.5	63.9	65.0	67.0	58.0
B.....	50.2	54.1	56.6	57.8	56.6
F.....	37.2	56.7	65.0	67.3	55.0
G.....	20.2	29.5	27.5	32.5	33.0
H.....	18.7	24.6	26.0	27.5	27.0
I.....	12.8	16.7	16.3	16.2	16.5
J.....	13.6	20.0	21.5	20.2	17.0
K.....	15.2	20.4	20.5	20.5	17.5
L.....	36.6	55.0	55.0	51.5	56.0
M.....	62.0	76.2	72.5	77.0	111.0
N.....	63.5	87.2	85.8	96.0	100.0
O.....	26.4	41.7	47.0	46.3	40.0
P.....	35.5	55.5	54.0	59.0	60.0
Q.....	61.0	96.0	93.2	96.5	117.0
R.....	29.3	41.7	47.0	49.4	36.8
S.....	23.7	35.7	33.8	37.0	41.0
T.....	17.7	24.8	20.2	28.3	21.5
U.....	10.8	22.5	22.2	23.5	19.3
V.....	15.7	21.2	21.2	23.5	22.0

Edsall and Dr. James H. Means in Boston. We are greatly indebted to Dr. Means for taking the measurements of this subject and for taking the mold of the surface and sending it to us to be measured.

## MEASUREMENTS OF THE BODY

The individual to be measured was undressed, weighed and placed on a flat table with a vertical foot-board about 30 cm. high. All the measurements were made with the subject flat on his back with his feet against the foot-board. A steel tape was used for all the linear meas-

urements and a cloth tape for the circumferences. The measurements actually used are given in Table 2; those not used are given in Table 3 in case other investigators wish to apply different formulas.

#### THE MOLD OF THE BODY

The method of determining the surface area finally adopted consisted in making a thin mold of the body, cutting this up in pieces which would lie flat, printing the patterns of these pieces on photo-

TABLE 3.—MEASUREMENTS NOT USED IN FORMULA

Index Number of Part Measured	Benny L.	Morris S.	R. H. H.	E. F. D. B.	Mrs. McK.
I.....	24.2 kg.	64.0 kg.	64.08	74.49	93.0
II.....	110.5 cm.	164.3 cm.	178.0	179.2	149.7
III.....	88.3	135.5	148.0	147.2	125.0
IV.....	81.1	124.6	136.5	135.5	.....
V.....	83.6	124.4	139.0	141.2	125.4
VI.....	76.5	115.2	130.0	125.5	107.0
VII.....	55.7	83.4	94.0	95.7	76.8
VIII.....	46.2	72.3	84.5	86.5	60.2
IX.....	65.1	83.5	80.7	84.5	92.0
X.....	40.0	60.2	81.5	67.5	55.5
XI.....	29.6	43.6	48.0	49.0	40.0
XII.....	8.2	11.3	.....	11.7	15.8
XIII.....	17.0	24.5	27.0	28.0	21.0
XIV.....	21.2	33.1	38.5	38.5	32.0
XV.....	18.6	27.5	25.3	30.0	30.5
XVI.....	17.8	26.0	25.0	29.0	30.0
XVII.....	35.5	50.3	48.0	56.5	56.0
XVIII.....	22.2	34.7	32.7	37.5	39.0
XIX.....	22.6	31.0	31.5	33.5	30.6
XX.....	43.2	52.0	48.0	52.5	35.5
XXI.....	28.5	38.0	36.0	37.0	34.2
XXII.....	74.5	108.0	99.0	107.0	106.0

graphic paper (Fig. 17) and finding the area of the printed patterns by cutting them out and weighing them. The subject was dressed in a tight-fitting suit of thin union underwear, which covered the body, arms and legs. Socks were put on the feet, thin cotton gloves on the hands, while over the head and neck was slipped a section of the leg of a knitted undersuit held in place by means of bandages. On this ground-work strips of paper were pasted until a flexible inelastic mold of the



body was completed. The material used was strong manila paper, about  $1\frac{1}{2}$  inches broad, gummed on one side. It is manufactured in large rolls and is used by stores as a substitute for string in doing up small packages and also by some tailors in making models of their customers. For our purposes it was wound in small rolls and placed in a small brass holder which moistened the gummed side as it was applied to the cloth covering the body. It could be applied so quickly that very little



Fig. 17.—Reduced photograph of the patterns printed from the mold of the head and neck of one of the subjects measured. The patterns of the head marked with one punch were cut out and weighed separately from the pieces of the neck marked with two punches. The dark areas were also weighed as control.

time was required to cover the body. The head presented no difficulty until the nose was reached. This region was the last to which the paper was applied and a couple of holes were left for the person to breathe through. The mold of the face was then quickly opened by means of curved bandage scissors. In most cases only one arm and one leg were measured.

TABLE 4.—COMPARISON OF AREAS OF PARTS OF BODY AS ACTUALLY MEASURED AND AS CALCULATED FROM FORMULAS

Part of Body	Benny L.			Morris S.			R. H. H.		E. F. D. B.			Mrs. McK.			
	Area as Measured, Sq. Cm.	Area as Calculated from Formula, Sq. Cm.	Error in Formula, Per Cent.	Area as Measured, Sq. Cm.	Area as Calculated from Formula, Sq. Cm.	Error in Formula, Per Cent.	Area as Measured, Sq. Cm.	Area as Calculated from Formula, Sq. Cm.	Error in Formula, Per Cent.	Area as Measured, Sq. Cm.	Area as Calculated from Formula, Sq. Cm.	Error in Formula, Per Cent.			
Head.....	900	888	- 1	1,030	1,064	+3	1,173	1,132	-4	1,154	1,192	+4	1,090	1,010	- 7
Arms.....	1,062	1,074	- 2	2,314	2,236	-3	2,524	2,535	+0	2,776	2,865	+3	2,298	2,351	+ 2
Hands.....	596	458	-23*	900	905	+1	968	977	+1	876	913	+5	678	690	- 3
Trunk.....	3,060	3,029	+ 6	6,304	6,318	+0	6,444	6,121	-5	6,572	6,264	-5	7,746	8,308	+ 7
Thighs.....	1,284	1,294	+ 1	3,022	3,207	+6	3,712	3,512	-5	3,820	3,655	-4	3,500	3,594	+ 3
Legs.....	930	973	+ 5	2,000	2,085	+4	2,396	2,225	-7	2,472	2,560	+4	2,156	2,113	- 2
Feet.....	611	596	- 3	1,150	1,123	-3	1,158	1,178	+2	1,330	1,378	+4	1,124	920	-18
Total.....	8,473	8,512	+ 0.5	16,730	16,938	+1.3	18,345	17,680	-3.8	19,000	18,832	+0.9	18,592	18,956	+ 2.0

\* Benny L. had chronic ulcers on his hands, and the measurement was made with difficulty. The hands of six other individuals were measured and calculated by the formula. The percentage of errors of the calculations in these cases were: -4.0, -1.8, +2.5, -1.8, +2.0 and -2.7.

The hands could not be covered satisfactorily with paper, and hard paraffin was used instead. This was melted and applied to the glove with a brush, soaking well into the meshes of the cotton. The melted paraffin was not too warm for the hands, but was uncomfortable for parts of the body which were not so accustomed to heat. Starch was tried in some instances, but dried too slowly; plaster-of-Paris was too stiff.

Certain portions of the skin were not measured by this mold. The area back of the ears was determined by tracing the back of the ears on a piece of cardboard and correcting by careful measurements. The skin between the toes was measured by tracing. The penis and scrotum were measured and the area determined geometrically. This left unmeasured only very small portions of the face and ears since the mold did not fit closely into the eye-sockets and the concavities of the ear. This error could not have amounted to more than 10 to 20 square centimeters in a total of fifteen thousand.

While the mold was still on the subject the landmarks of the body were located through the paper and the different anatomical regions marked off by drawing the borders on the paper. The mold was then removed with bandage scissors or small probe pointed scissors and the inside of the cloth covered with a thin layer of melted paraffin which, when it hardened, left a material much easier to work with than the cloth and paper alone, since this would not lie flat. Next the mold was cut at the borders of the various regions of the body and each of these regions cut into pieces which would lie flat. These pieces were then marked with a punch for identification and transferred to a large photographic printing frame. After printing in the sun and without developing or fixing, patterns of the pieces of the mold were cut out and weighed to the tenth of a milligram and the blank parts of the sheet weighed as a control. Before this printing each sheet of photographic paper was carefully measured and weighed and the area of each gram of paper determined. By weighing the patterns of each region together it was a simple matter to find the area of that region. A copy of the print made from the mold of the head and neck of one of the subjects is given in Figure 17 showing the method of cutting the paraffined mold so that it would lie flat.

#### ACCURACY OF METHOD

The accuracy of the procedure was tested in several ways. The bottom of a porcelain evaporating dish was measured twice with a difference of 0.1 per cent. between the two measurements. The surface of the hand of D.D.B. was measured three times, the glove being covered once with starch and on the two other occasions with paraffin.

The square centimeters of surface area as determined on the three occasions were 555.5, 556.0 and 555.5. The right and left sides of the whole body of Benny L. measured separately, agreed within 0.5 per cent.

#### MEASUREMENTS

The body was divided into the larger regions used by Meeh. An effort was made to select the measurements which represented the length and average breadth of the part. The head region included the ears and the trunk included the neck, the breasts in the female, and the penis and scrotum in the male.

#### DETERMINATION OF NEW FORMULA

Having measured the surface areas of the different parts of the body and the linear measurements of these parts, the formula to determine the surface area of each part was calculated as follows: the various measurements of length were multiplied by various sums of the measurements representing the width; the resulting figure was divided by the surface area as actually measured. The factors resulting from this calculation in each of the five individuals were compared to determine the percentage variation. That particular combination of length and breadth measurements which showed the smallest variation was chosen and the reciprocal of the average factor for this combination taken as a constant. Fortunately the best results were always obtained by using measurements which were simple. The factors include the multiplication by two necessary to give the area of the right and left arm, hand, etc.

#### MEASUREMENTS USED IN FORMULA (TABLE 2).

HEAD: AB 0.308.

A—Around vertex and chin.

B—Around occiput and forehead, just above eyebrows.

ARMS: F(G + H + I) 0.558.

F—Outer end of clavicle to lower border of radius.

G—Circumference at level of upper border of axilla.

H—Largest circumference of forearm.

I—Smallest circumference of wrist.

HANDS: JK 2.22.

J—Lower posterior border of radius to tip of second finger.

K—Circumference of open hand.

TRUNK: L(M + N) 0.703.

L—Suprasternal notch to upper border of pubes.

M—Circumference of abdomen at level of umbilicus.

N—Circumference of thorax at level of nipples in the male, and just above breasts in the female.

THIGHS: O(P + Q) 0.508.

O—Superior border of the great trochanter to the lower border of the patella.

P—Circumference of thigh just below the level of the perineum.

Q—Circumference of hips and buttocks at level of trochanters.

LEGS:  $RS$  1.40.

R—From sole of foot to lower border of patella.

S—Circumference at level of lower border of patella.

FEET:  $T(U + V)$  1.04.

T—Length of Foot.

U—Circumference of foot at base of little toe.

V—Smallest circumference of ankle.

#### MEASUREMENTS NOT USED IN FORMULA (TABLE 3)

I—Weight.

II—Height.

III—Sole of foot to suprasternal notch.

IV—Sole of foot to level of nipples.

V—Sole of foot to upper border of axilla.

VI—Sole of foot to tip of ensiform process.

VII—Sole of foot to superior border of great trochanter.

VIII—Sole of foot to perineum.

IX—Circumference of body at level of tip of ensiform.

X—Tip of second finger to upper border of axilla.

XI—Tip of second finger to tip of olecranon process.

XII—Tip of second finger to metacarpo-phalangeal joint.

XIII—Tip of olecranon to lower border of radius.

XIV—Tip of olecranon to outer end of clavicle.

XV—Circumference of arm at the insertion of the deltoid.

XVI—Circumference of arm at belly of biceps.

XVII—Circumference of thigh half way between anterior superior spine of the ilium and the lower border of the patella.

XVIII—Largest circumference of calf.

XIX—Circumference of foot around heel.

XX—From back of neck around superior maxilla just below ears and nose.

XXI—Around neck just below larynx.

XXII—Around shoulders at level of heads of humeri.

#### BORDERS OF REGIONS OF BODY:

Head: Lower margin of the mandible to its posterior border, thence to tip of the mastoid process and in a straight line to the external occipital protuberance.

Arm: From the acromion process anteriorly and posteriorly to the upper border of the axilla.

Hand: Line at right angles to long axis of forearm drawn at level of tip of ulna.

Thigh: From the perineal point going posteriorly in the natal fold to the upper border of the great trochanter, thence medially in a straight line to the perineal point.

Leg: Line at level of lower border of patella.

Foot: Line at level of tip of lateral malleolus.

#### DISCUSSION OF RESULTS

Table 1 shows that the constant employed by Meeh has not been confirmed by subsequent observers. It gives results which are too high in every case except one very thin woman. Lissauer found Meeh's figure for infants 16 per cent. too high. Bouchard in four of his five cases found it from 2 to 33 per cent. too high, while in our five cases we have found it from 7 to 36 per cent. too high. The majority of Meeh's

subjects seem to have been thin, and the error of the formula is very great in fat individuals. One can perhaps obtain fairly accurate results in using Meeh's formula if one retains the factor of 12.3 for thin subjects, 11 to 12 for people of average build, 10 to 11 for the moderately stout and 9 to 10 for the very fat. Possibly at some later date a more accurate factor can be determined by the relationship of weight to height, retaining Meeh's fundamental principle of the  $\frac{2}{3}$  power of the weight.

Miwa and Stöltzner's formula gives results only slightly better than Meeh's. The errors in calculated areas of our five subjects using their formula are as follows: Benny L. + 18 per cent., Morris S. + 17 per cent., R. H. H. + 8 per cent., E. F. D.B. + 18.5 per cent., Mrs. McK. + 26.5 per cent. If the constant of 3.84 were used instead of 4.5335 the results would be much better for this series.

The series of five individuals measured by us is perhaps too small to determine factors which will remain unaltered by subsequent research, but it is doubtful if the changes will be of significance. The range of body shape among our subjects was, however, very great, and the error of the factors comparatively small. The principle of the method has been demonstrated to be sound. Unfortunately, it involves the taking of nineteen measurements, a matter of perhaps fifteen minutes time. Subsequent investigation may reduce the number, but it is difficult to see how one can avoid measuring each part of the body if one wishes to obtain accurate results on people whose shapes do not correspond closely to the average.

In any discussion as to whether metabolism is proportional to body weight or to surface area it is essential to apply a method of measuring the surface which does not depend entirely on weight. The key to the question may perhaps be found in those individuals whose surface area is not proportional to the  $\frac{2}{3}$  power of their weight, multiplied by a constant determined by measurements of average individuals.

#### SUMMARY AND CONCLUSIONS

The discussion of the relationship of metabolism to surface area has been based almost entirely on Meeh's formula as determined in 1879. Subsequent observers have found a consistent plus error in this formula amounting to as much as 36 per cent. in the case of very fat individuals.

The surface area of the various parts of the body can be determined as follows: A mold of the surface is made by pasting paper over tight-fitting underwear. The area of the mold is then determined by cutting it in pieces, printing a pattern on photographic paper, cutting out the pieces of the pattern and weighing them.



To determine the area of each part of the body by linear measurements alone a formula has been devised on the principle of length times the average breadth times a constant. The sum of these parts gives the total surface area of the body.

Five individuals of widely varying shapes have been measured and the surface area as calculated from the formulas compared with the surface area as actually measured. In the five cases the average error was 1.7 per cent.

In discussing the question as to whether the basal metabolism is proportional to surface area or to weight it is preferable to determine the surface area by a formula which is not of necessity a function of the weight.

NOTE.—Since this article was submitted for publication the formula has been tested on a tall and exceedingly thin boy, 18 years old. This patient, Gerald S., came to the hospital much emaciated from diabetes and was kept for eleven days practically without food, receiving only whisky. The mold of the body was taken on Dec. 1, 1914, shortly after his fast. At this time he weighed 45.25 kg. His surface area according to Meeh's formula was 1.563 square meters. The mold was kindly measured for us by Miss Margaret Sawyer who obtained the following figures:

	Actual Area as Measured sq. cm.	Area as Calculated from Formula sq. cm.	Error in Formula Per Cent.
Head.....	950	978	+ 3
Arms.....	2,052	2,047	— 0
Hands.....	847	875	— 0
Thighs.....	3,002	2,677	—11
Trunk.....	5,003	4,158	—17
Legs.....	1,876	2,144	+14
Feet.....	1,042	1,055	+ 1
Totals.....	14,801	13,934	— 5.8

## CLINICAL CALORIMETRY

### SIXTH PAPER

#### NOTES ON THE ABSORPTION OF FAT AND PROTEIN IN TYPHOID FEVER\*

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In the course of other work on metabolism in typhoid fever it became advisable to analyze the feces of the patients. While these analyses constitute only a part of the problem in hand, the paucity of studies on the absorption of food in the febrile state appears to warrant publication of the results as a separate communication. For a complete discussion of the absorption of food in typhoid fever the reader is referred to the paper of Du Bois.<sup>1</sup>

Seven cases in all have been studied. The diets administered were modifications of the high calory diet employed in this clinic, that is, the proportions of fat and carbohydrate were varied to satisfy the requirements of the problem under investigation.

#### METHODS OF CHEMICAL ANALYSIS

Urine and feces were collected in the manner described by Gephart and Du Bois.<sup>2</sup> The analysis consisted in the determination of fat and nitrogen in the feces and total nitrogen in the urine. Nitrogen was determined in all cases by the well known Kjeldahl method, fat in the feces was determined in part by the Kumagawa-Suto method, and later by a saponification procedure described by one of us.<sup>3</sup> Carbohydrate in the feces was not determined (see work of DuBois).

#### CLINICAL DATA

All of the patients were admitted to Bellevue Hospital during 1913. As is customary on the service, each patient was given an enema every morning. Except when otherwise stated, the patients had from one to two formed or semiformal stools a day.

Emil C., aged 22 years, was admitted August 23, the fifth day of the disease. Widal reaction and blood culture positive. Illness, severe. The original fever lasted twenty-three days. After two days of normal temperature, the patient developed a severe relapse of twenty days' duration.

Thomas B., aged 60 years, admitted October 2, the fifteenth day of the disease. Widal reaction and blood culture positive. Illness, mild. Duration

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\* From the Russell Sage Institute of Pathology, in Affiliation with the Second Medical Division of Bellevue Hospital.

1. DuBois, E. F.: *THE ARCHIVES INT. MED.*, 1912, x, 177.

2. Gephart, F. C., and DuBois, E. F.: *The Organization of a Small Metabolism Ward*, p. 829.

3. Gephart and Csonka: *On the Estimation of Fat in Feces*, *Jour. Biol. Chem.*, 1914, xix, 521.

TABLE 1.—DAILY AVERAGES OF PERIODS

Patient and Weight	No. of Period	Stage of Typhoid Fever	Dates and Days of Disease, Inclusive	Range of Maximum Temp. F.	Food Intaking Period, Averages per Day			Analysis of Feeds, Average per Day			Percentage Loss in Feeds	
					Carb., Gm.	Fat., Gm.	Nitrogen, Gm.	Fat, Gm.	Nitrogen, Gm.	Fat	Nitrogen	
Paul C. 60.2 Kg.	1	Early and late steep curve.	Sept. 11-16 (25-30)	100.6-102.6	162	210	14.9	6.67	1.19	2.9	8.0	
	2	Late steep curve.	Sept. 17-21 (31-35)	99.8-101.0	485	71	15.0	6.30	2.89	8.5	19.5	
	3	Relapse	Sept. 22-Oct. 3 (36-47)	100.0-104.8	331	127	13.6	2.53	1.24	2.0	9.1	
	4	Ascend. Temp. and early steep curve.	Oct. 4-7 (48-50)	102.0-104.0	174	225	15.0	7.85	2.31	3.5	15.4	
Thomas B. 71.5 Kg.	1	Contin. Temp.	Oct. 7-10 (20-23)	103.0-104.0	164	211	15.0	9.19	2.09	4.4	12.9	
	2	Early steep curve.	Oct. 11-13 (24-26)	102.4-103.0	479	71	14.9	5.80	1.89	8.2	12.5	
	3	Late steep curve.	Oct. 14-16 (27-29)	101.0-102.0	157	204	13.8	5.02	1.58	2.5	9.3	
	4	Late steep curve.	Sept. 17-21 (24-28)	100.8-101.8	483	74	15.0	7.04	2.38	9.5	15.9	
Christian M. 58.8 Kg.	1	First week conval.	Sept. 22-25 (29-32)	99.0-99.6	160	210	15.1	6.85	1.62	3.3	10.7	
	2	First week conval.	Sept. 26-28 (33-35)	99.0-99.4	431	165	16.6	7.69	1.97	4.6	11.9	
	3	First week conval.	Sept. 29-33 (18-21)	101.2-103.0	160	212	15.4	7.08	1.83	3.3	11.9	
Ernest H. 91.9 Kg.	1	Early steep curve.	Sept. 24-27 (22-25)	100.4-101.6	479	71	15.0	3.75	1.67	5.3	11.1	
	2	Late steep curve.	Sept. 28-Oct. 1 (26-29)	99.8-100.0	296	286	15.3	6.53	1.47	2.3	9.6	
	3	First week conval.	Oct. 7-10 (16-19)	103.8-104.6	47	273	15.0	6.61	1.37	2.4	9.1	
Anton K. 200.7 Kg.	1	Contin. temp. and early steep curve.	Oct. 11-16 (20-25)	99.8-102.8	386	56	12.0	3.33	1.54	7.0	10.3	
	2	Early and late steep curve.	Oct. 17-25 (18-26)	101.0-104.2	385	57	14.3	1.63	0.84	2.9	5.8	
Richard T. 26 Kg.	1	Early steep curve.	Oct. 30-Nov. 5 (20-26)	102.2-104.0	399	143	15.6	9.74	2.60	6.8	14.8	

of original fever, thirty-one days. After fourteen days of normal temperature the patient developed a relapse which lasted twenty days. The relapse was complicated by acute fibrinous pleurisy.

Christian M., aged 31 years, admitted September 8, the fifteenth day of the disease. Widal reaction and blood culture positive. Illness, mild. Duration of fever thirty days.

Ernest H., aged 30 years, admitted September 16, the fourteenth day of the disease. Blood culture and Widal reaction negative, though clinically the disease was undoubtedly typhoid fever. The illness was mild, the fever lasting twenty-four days.

Anton K., aged 18 years, admitted September 30, the ninth day of the disease. Blood culture positive. Illness, severe. Duration of fever twenty-five days. The patient suffered from diarrhea from the eleventh to the sixteenth day, passing three to nine stools a day. The first period of the analyses was not begun until the diarrhea had ceased.

Richard T., aged 14 years, admitted October 6, the seventh day of the disease. Widal and blood culture positive. Illness, severe. Duration of fever twenty-eight days. Mild cholecystitis developed on the twenty-fifth day. After one day of normal temperature a relapse occurred which lasted one week.

Morris S., aged 21 years, admitted October 17, the seventh day of the disease. Blood culture positive. Illness severe. Duration of fever thirty-four days. The patient suffered two relapses, the first severe, beginning on the thirty-sixth day and lasting twenty days; the second mild, beginning on the sixty-eighth day and continuing nine days.

TABLE 2.—DAILY AVERAGES AND PERCENTAGE LOSS

Stage of Disease	No. of Periods	Av. Food Fat Gm.	Average Daily Loss		Percentage Loss	
			Fat, Gm.	Nitrogen, Gm.	Fat	Nitrogen
Cont'd temperature .....	3	204	6.11	1.20	2.9	10.7
Low fat, steep curve.....	6	67	4.74	1.82	6.9	12.5
High fat, steep curve.....	5	199	7.15	1.84	3.8	11.9
Convalescence .....	3	220	6.99	1.69	3.4	10.7
Totals .....	17	...	6.25	1.57	4.3	11.2

## DISCUSSION OF RESULTS

In Table 1 the results are expressed in terms of daily averages for the periods, which lasted from three to twelve days. The stage of the disease is designated by a description of the character of the temperature curve rather than by the actual day of the illness. As in previous papers, the stage of ascending temperature corresponds to the "first week," that of continued temperature to the "second week," that of the early steep-curve to the "third week," and that of the late steep-curve to the "fourth week." In the last two columns the losses are expressed in terms of percentage.

A summary of all the periods, in daily averages according to the stage of the disease, is given in Table 2.

## ABSORPTION OF FAT

The total fat in the stools varied from 1.63 to 9.74 gm.

The mere statement of the amounts, however, conveys but little information; the stage of the disease and the quantity of fat in the food must be taken into consideration for a complete interpretation of the results. Likewise it should be stated that the expression of the results in percentage values is apt to be misleading unless one bears in mind that even the stools of fasting persons contain fat.

In the ascending and continuous temperature stages when the fat in the food varied from 127 to 273 gm. the total fat lost was from 2.53 to 9.19 gm. The percentage loss varied from 2.0 per cent. to 4.4 per cent.

The average total loss for this stage of the disease was 6.11 gm.; the average percentage loss was 2.9 per cent.

The results in the early and late steep-curve stages fall into two groups, according to the amount of fat which the patient received in his food.

Patients receiving from 56 to 74 gm. lost in the stools from 1.63 to 7.04 gm. of total fat, with an average loss of 4.4 gm. Attention should be directed to the unusually small loss of 1.63 gm. when the patient received 57 gm. The average percentage loss for this group was 6.9 per cent.

With patients receiving from 143 to 225 gm. of fat in the food, the total loss varied from 5.02 to 9.74 gm., with an average loss of 7.15 gm. In this group the relatively large loss of 9.74 gm. when the patient took only 143 gm. in the food should be noted. The average percentage loss for the group was 3.8 per cent.

In convalescence the total fat intake varied from 165 to 286 gm. The fat loss varied from 6.53 to 7.60 gm. The percentage loss was from 2.3 per cent. to 4.6 per cent.

If only those periods be considered in which the fat intake was relatively large, the percentage fat loss in the stools for all stages of the disease was 3.5 per cent. The loss in the febrile stage was 3.3 per cent., in convalescence it was 3.4 per cent. In other words, the patients in this series absorbed fat as well in the febrile stage of the disease as in convalescence.

The average fat loss for all the patients in all stages of the disease amounted to 4.3 per cent. This result is somewhat lower than that obtained by Du Bois, who found the average percentage loss to be 6.02 per cent. When the results are considered as a whole the conclusion appears to be warranted that fat is almost completely absorbed when given in very large quantity.

## THE ABSORPTION OF PROTEIN

The quantity of protein in the diet was kept as nearly uniform as circumstances permitted. The lowest daily average intake of nitrogen was 12.0 gm., the highest was 16.6 gm.

The total nitrogen in the stools varied from 0.84 to 2.89 gm. The average total nitrogen for all stages of the disease amounted to 1.57 gm. The highest average loss, according to periods, of 1.84 gm. a day occurred in the steep-curve stage. The smallest average loss of 1.20 gm. occurred in the stage of continued fever. The quantity of fat in the food appeared to be without influence on the nitrogen loss.

The average percentage loss of nitrogen according to periods varied from 10.7 per cent. to 12.2 per cent. The average percentage loss for all stages of the disease was 11.2 per cent. This result is higher than that obtained by Du Bois, which amounted to 7.1 per cent. No explanation of this difference has been found.

## SUMMARY

The feces of seven typhoid patients on the high calory diet have been analyzed for fat and protein in seventeen periods of three to twelve days each in length.

The average total fat loss for all the periods was 6.25 gm., corresponding to a percentage loss of 4.3 per cent. No differences were observed in the percentage absorption of fat in the early and later stages of the fever or up to the end of the first week of convalescence, when the intake was relatively large.

The average total nitrogen loss for all the periods amounted to 1.57 gm., corresponding to a percentage loss of 11.2 per cent.

The constant presence of fat and nitrogen in the feces, even in fasting, vitiates to some extent the validity of the results when expressed in percentages.



# CLINICAL CALORIMETRY

## SEVENTH PAPER

### CALORIMETRIC OBSERVATIONS ON THE METABOLISM OF TYPHOID PATIENTS WITH AND WITHOUT FOOD \*

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#### CONTENTS

1. Previous investigations.
2. Methods used.
3. Case histories.
4. Experimental data.
5. Discussion of results.
  - A. The law of the conservation of energy in fever.
  - B. The basal metabolism in typhoid fever.
  - C. The specific dynamic action of food in typhoid fever.
  - D. The relationship of heat production and heat elimination.
  - E. A comparison of caloric intake and caloric output.
  - F. Summary and conclusions.

#### PREVIOUS INVESTIGATIONS

In a previous communication<sup>1</sup> the respiratory metabolism of typhoid patients as determined by means of the small Benedict respiration apparatus was discussed in detail. The literature of the subject was also reviewed, making repetition here unnecessary. Following this earlier work it was possible to continue the study of the typhoid patients by using the respiration calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital. In the immediately preceding papers of the series<sup>2</sup> the calorimeter and the metabolism ward have been described in detail and data have been given in regard to the normal controls and the absorption of food in typhoid fever. The patients studied were all in the metabolism ward and the calorimeter experiments were conducted in the manner described in the paper on normal controls. In our previous work on the general effect of the high calory diet on respiratory metabolism it was difficult to control the nourishment of the patients so as to determine the basal metabolism and the quantitative effects of different foods. It was, however, pos-

\* Submitted for publication Feb. 10, 1915.

\* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital, New York.

1. Coleman and DuBois: The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever, *THE ARCHIVES INT. MED.*, 1914, xiv, 168

2. Clinical Calorimetry, Papers 1 to 6, this number. Brief preliminary reports were published in *Jour. Am. Med. Assn.*, 1914, lxiii, 827, and *ibid.*, 1914, lxiii, 932.

sible to demonstrate that the heat production of typhoid patients on a liberal diet was practically the same as that of fasting patients.

Patients with fever have been studied before in various calorimeters. Isaac Ott<sup>3</sup> of Philadelphia as early as 1892 made observations on a patient with malaria using a rather simple type of calorimeter which required a plus correction of 16 per cent. Likatscheff and Avroroff<sup>4</sup> in 1902 made classical experiments on a similar case. In 1909 Benedict and Carpenter<sup>5</sup> studied a few cases of mercurial poisoning with fever in the Middletown calorimeter. An excellent summary of the literature is given in the Russian publication.<sup>4</sup> It is sufficient to say that the rise and fall of body temperature have been ascribed at various times to every possible combination of increase and decrease in heat production and heat elimination. The Russians used the Paschutin calorimeter in which the patient was kept for twenty-two hours, feeding herself and apparently moving about the chamber during the day whenever she felt inclined to do so. The heat elimination was measured in periods of two hours each and the body temperature was determined every two hours, apparently by means of a mercurial thermometer in the axilla. The CO<sub>2</sub> and water elimination were measured in two-hour periods but the oxygen consumption and consequently the respiratory quotient could only be determined by the change in body weight during twenty-two hours. This method seems to have given satisfactory results, since the quotients correspond to those usually found under similar conditions and calculation of the indirect calorimetry in the three experiments gives results which come within -6 per cent. +6 per cent. and +12 per cent. of the direct calorimetry. The Russians themselves calculated the total heat production by adding the calories stored in or lost from the body as the temperature rose and fell to the calories eliminated by means of radiation, conduction and vaporization. They came to the conclusion that the rise of body temperature was due to an increase in heat production. Benedict and Carpenter studied their fever patients under similar conditions, but determined the oxygen, CO<sub>2</sub>, and the heat elimination in periods from two to six hours in length. If one takes the periods when their subjects

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3. Ott, Isaac: *The Modern Antipyretics*, Ed. 2, Easton, Pa., 1892; *Fever, Its Thermotaxis and Metabolism*, New York, 1914.

4. Likatscheff and Avroroff: *Investigations of Gaseous and Heat Exchange in Fevers*. Reports of the Imperial Military Academy, St. Petersburg, 1902, v, parts 3 and 4. We are indebted to Dr. F. G. Benedict of the Carnegie Nutrition Laboratory for permission to consult his translation of this important work. Excellent abstracts in English have been published in a paper by A. I. Ringer (*Physiology and Pathology of Fever*, *Am. Jour. Med. Sc.*, 1911, cxlii, 485) and in the monograph on *Fever* by Ott.

5. Benedict and Carpenter: *Preliminary Observations on Metabolism During Fever*, *Am. Jour. Physiol.*, 1909, xxiv, 203.

had a body temperature of 38 C. or over and calculates the indirect calorimetry, using the oxygen and quotients, it is easy to determine the divergence of the direct from the indirect calorimetry. The percentage differences are as follows: +5. +10. -9 +9. +2.

#### METHODS USED

The present work with the calorimeter was undertaken to extend the previous observations and clear up some doubtful points which could be settled only by a most careful control of the diet and by a comparison of the direct and indirect calorimetry. The fact that it was impossible to bring typhoid patients into nitrogen equilibrium unless the diet greatly exceeded the heat production as calculated from the oxygen consumption, suggested the possibility that the method of calculating the indirect calorimetry might be incorrect. There remained also the old work on fever in which abnormally low respiratory quotients were obtained, leading several investigators to believe that the metabolism in fever was radically different from that in health. Finally, it was hoped that it would be possible to determine whether the rising body temperature was due to an increasing heat production or to a decreasing heat elimination.

The subjects studied were typhoid patients who entered Bellevue Hospital in 1913 and 1914. There was some selection of cases in an effort to obtain men in the early stages of the disease who were intelligent enough to cooperate. Most of the patients were taken to the metabolism ward so early in the disease that it was impossible to predict whether the fever would run a mild or severe course. Several patients were transferred from the First Medical Division through the kindness of Dr. Norrie and Dr. Miller to whom we are much indebted.

All of the patients were put on the high calory diet described in previous publications<sup>6</sup> and trained to take the large amounts of food. The very large amounts formerly given to some patients were not administered and the calories seldom exceeded 3,000 a day. An attempt was made to keep the food nitrogen at 15 grams. The stools exceeded two a day only on the occasions mentioned in the histories, and there was seldom abdominal distention. None of the patients was tubed, although cold sponges were occasionally given to make the patient

6. Shaffer and Coleman: Protein Metabolism in Typhoid Fever, *THE ARCHIVES INT. MED.*, 1909, iv, 538-600; Coleman: Diet in Typhoid Fever, *Jour. Am. Med. Assn.*, 1909, liii, 1145; The High Calory Diet in Typhoid Fever—A Study of One Hundred and Eleven Cases, *Am. Jour. Med. Sc.*, 1912, cxliv, 659; DuBois: The Absorption of Food in Typhoid Fever, *THE ARCHIVES INT. MED.*, 1912, x, 177; Coleman: Weight Curves in Typhoid Fever, *Am. Jour. Med. Sc.*, 1912, cxliv, 659; Diet and Metabolism in Fever, *Trans. Fifteenth Internat. Cong. on Hyg. and Demog.*, 1912.

feel more comfortable when the temperature reached 104. Nervous symptoms were not prominent in any case, although one or two of them were mildly delirious for a few days. Most of the patients were cheerful throughout their illness and read the daily papers. It is estimated that their activity increased their metabolism about 10 per cent. above the basal level, although this figure is necessarily only an approximation.

#### CASE REPORTS

CASE 1.—Morris S. (severe typhoid) tailor, English Hebrew or Russian extraction, 21 years old, admitted October 17, discharged January 30.

*History.*—Previous history unimportant; patient is not alcoholic. He landed from England Sept. 28, 1913. October 10 he began to suffer from pain in his abdomen, chest and back. On the thirteenth he had a nose bleed. Since the onset of symptoms he has had no appetite and has been constipated.

*Physical Examination.*—Patient is a well-nourished young man of small frame and short stature, being 164 cm. tall. There is slight cyanosis of lips and ears, the tongue is heavily coated, tonsils hypertrophied and congested. There is an occasional subcrepitant râle at the apex of the left lung. The spleen is palpable.

Blood taken October 18 gave a negative Widal test but developed a growth of typhoid bacilli. The spleen edge was felt 4 cm. below the costal margin and a few rose spots were present. October 24 the Widal was positive. The next day there were a few sibilant and sonorous sounds over the chest, clearing up by the twenty-seventh. The patient had been on a diet with high carbohydrate and low fat, and on October 23 and 24 had shown abdominal distention with about four liquid stools a day. The distention and diarrhea ceased when the fat was increased and the very large amounts of carbohydrate stopped. For the next month he had only one or two movements a day. October 30 he became a little irrational and his color was grayish, his pulse soft and very dicrotic. November 3 he was irrational in the calorimeter and wrote several notes about the animals which he saw in his hallucinations. The next day he was in much better condition, the pulse was stronger and his physical condition improved steadily.

November 16 the temperature began to rise after it had been practically normal for five days. He felt perfectly well and was bright and cheerful, in spite of a temperature of 104, until the evening of the eighteenth when he had a sharp pain in the right side of the abdomen. This disappeared the next day. This relapse was almost as severe as the original infection, but the patient was not quite so toxic and was never irrational. The temperature remained normal from December 7 to 17. From November 23 to 26 he had frothy stools but these became formed once more when the fat in the diet was increased.

December 17 a second relapse began and lasted until the 27th. During the period of rising temperature he was somewhat apathetic and suffered from headache and was fretful during the two days of high fever. His general condition remained excellent and he never realized that he was having a relapse. Following this, convalescence was rapid, since he had lost practically no weight during his illness. During the next year he reported at the hospital several times, always in excellent condition and five or ten pounds heavier than ever before in his life.

In December, 1914, he returned to the metabolism ward for two days, giving us the opportunity to determine his basal metabolism and the specific dynamic action of the protein meal.

This history is given in detail since Morris S. was placed in the calorimeter twenty-four times. He was an exceptional patient, in that he ate the prescribed diet practically every day and enjoyed the distinction of going in the calorimeter more often than his fellow patients. Nothing made him happier than the extra attention he received on calorimeter days, and as a result he did exactly what he was told to do. We were particularly fortunate in being able to determine the specific dynamic action of protein and the basal metabolism while he was in perfect health, a year after his infection.

**CASE 2.**—Charles F. (severe typhoid), elevator constructor, born in New York, 24 years old, admitted November 4, discharged January 12.

*History.*—Lives in same house as his nephew Howard F., who has similar symptoms. On October 28 he began to suffer from anorexia, malaise and headache. On November 3 he had a nose bleed. He did not take to bed until admitted to the hospital.

*Physical Examination.*—Fairly well-nourished young man of medium frame, 166 cm. tall. He is moderately prostrated; there are several rose spots and the spleen edge is palpable 4 cm. below the costal margin.

Blood taken the day after admission gave a positive Widal test and showed a growth of typhoid bacilli. November 7 and again on the eighth he had a small intestinal hemorrhage of about 200 c.c. His general condition remained fair; he was rational and the toxemia not marked. He was given a daily sponge for his high temperature. At this time he took his food very badly and after the hemorrhages ceased it was impossible to give even 2,000 calories. November 14 to 17 he had a severe follicular tonsillitis and his toxemia was marked. Rose spots appeared in crops. On the nineteenth he had a hemorrhage of about 250 c.c. and was very toxic and apathetic for the next week. His pulse was very soft, systolic blood pressure being 95 mm. mercury. By December 3 the temperature was normal, he was much improved and was reading the paper every day. Convalescence was rapid. Throughout the disease he had one formed stool each day.

This patient was very intelligent and was anxious to help us in every way possible but his digestion made it difficult for him to take the food. He was very quiet while in the calorimeter.

**CASE 3.**—Howard F. (typhoid fever of moderate severity), schoolboy, born in New York, 12 years old, admitted November 4; discharged January 22.

*History.*—Lives in the same house as his uncle, Charles F. He was perfectly well until October 26 when he had a severe headache. On the twenty-eighth he felt so sick that he took to bed. The next day he had a chill; vomited. He had nose bleed on the thirty-first and on the day of admission.

*Physical Examination.*—Patient is a tall, slender boy who has not yet reached the age of puberty; height 160 cm.; the cheeks are flushed and he looks acutely ill. Heart apex in the fourth space 8.5 cm. to the left of the midline. There are several rose spots on the abdomen; the spleen is not palpable.

On November 14 the blood culture showed typhoid bacilli. November 12 showers of subcrepitant râles appeared at the left base and the next day sibilant and sonorous sounds were heard all over the chest. His general condition was good, and although he was very apathetic, he was perfectly rational. He took his food very poorly, vomiting often. By the seventeenth he was very thin, quite toxic, very drowsy but rational. The pulse was soft but of fair quality.

The sibilant and sonorous sounds persisted until the twenty-fourth, by which time the temperature was falling, the appetite much better and the patient able to read the paper. Convalescence progressed rather slowly. On December 10 he passed two ascarides. The heart action was rapid on exertion and on the eighteenth the apex was in the fourth space 9.5 cm. from the midline. He left the hospital in good condition. Throughout his illness he had one stool a day.

The boy was very intelligent and made a good subject for the calorimeter.

CASE 4.—Karl S. (typhoid fever of moderate severity), stoker on steamer to South America, German, 24 years old, admitted December 29; discharged Feb. 18.

*History.*—Returning on a voyage from Brazil he landed at San Domingo for a few days, reaching New York December 20. Two days later he began to suffer from headache, weakness, lassitude, anorexia and nausea. On the twenty-fourth he began to have daily chills.

*Physical Examination.*—One hundred and sixty-eight cm. tall, muscular and well nourished. His face is flushed and he looks stuporous. No spots, spleen not palpable. Blood taken the day after admission gave a negative Widal but positive growth of typhoid bacilli. January 1 rose spots appeared and the spleen became palpable. On the third he was prostrated, apathetic and showed slight subsultus tendinum. The pulse was soft and dicrotic and the abdomen distended. When carbohydrates were pushed too high he became distended, but this trouble disappeared when the amounts were decreased. By January 7 he was anxious about his condition and easily frightened. On the tenth his condition was satisfactory and by the twenty-sixth he was afebrile and was reading and studying every day. He was very hungry during his rapid convalescence. February 14 he developed tonsillitis. The temperature rose to 101 and the pulse became rapid. He did not feel sick and resented being confined to bed. On the seventeenth he became insubordinate and was discharged from the hospital. Two weeks later he returned on a visit in good condition.

This patient was a rough sailor of sullen disposition and made a rather restless subject for the calorimeter. During most of the observations on this man one of the water thermometers was being repaired and the method of direct calorimetry could not be used.

CASE 5.—Thomas B. (typhoid fever, mild; followed by acute fibrinous pleurisy). Laborer, Irish, 60 years old, admitted October 2, discharged December 8.

*History.*—Moderately alcoholic. About September 18 began to suffer from malaise, anorexia and fever.

*Physical Examination.*—Large well-nourished man, who looks acutely ill. He is apathetic and slightly cyanotic.

Blood taken the day of admission gave a positive Widal and showed a growth of typhoid bacilli. Many rose spots appeared but the spleen was never palpable. He took his food well and was never very ill. From October 22 to November 6 the temperature was normal. Then it rose gradually to 104 and fell slowly reaching normal on the twenty-sixth. During this time he developed dulness, bronchial voice and breathing at the left base, the signs being attributed to a pleurisy rather than pneumonia. He made a rapid convalescence.

CASE 6.—Richard T. (mild typhoid). Mulatto boy, born in New York, 14 years old, admitted October 6, discharged November 24.

*History.*—About September 30 began to suffer from headache, weakness, constipation and occasional abdominal pains.



*Physical Examination.*—Well nourished active boy who has not yet reached puberty. There are a few rose spots and the spleen is palpable.

The day after admission the blood culture gave a positive Widal and showed a growth of typhoid bacilli. The disease ran a mild and uneventful course, in spite of high evening temperatures, until October 25, when he developed slight pain and tenderness over the gall bladder, lasting two days. The temperature reached normal October 29, but rose again in a mild relapse lasting till November 6. Convalescence was rapid.

The boy was somewhat mischievous and was very active throughout his stay in the hospital. While in the calorimeter he spent most of his time looking out of the window and was not as quiet as most of the patients.

CASE 7.—Anton K. (mild typhoid), factory worker, Austrian, 18 years old, admitted September 30, discharged November 18.

*History.*—September 22 he began to have daily chills and fever, lost his appetite, felt exhausted and had severe pains in the epigastrium.

*Physical Examination.*—This showed a well-nourished man, apathetic and acutely ill. Typhoid bacilli were found in the blood. At the height of his fever he was prostrated and developed slight subsultus tendinum. He took his food well and was in good condition on October 16, the first day of normal temperature.

CASE 8.—Rose G. (severe typhoid), born in New York, 12 years old; admitted September 19, discharged November 26.

*History.*—Menstruation has not yet begun. The girl is tall and very thin and is somewhat deficient mentally. She went through a severe course of typhoid, with marked emaciation. Blood culture showed typhoid bacilli. During the disease she had rales at both bases and developed bed sores because she had all her life been incontinent of urine. Temperature reached normal October 29, and she was up and about on November 17. During convalescence she ate enormous amounts of food, with very slight gain in weight. She was not in the metabolism ward and exact figures for the food were not obtainable, but it seemed as if the discrepancy between food and gain in weight could be accounted for only by a greatly increased metabolism. The first hour she was in the calorimeter she was quiet, but during the second hour she voided in bed and began to cry, making it necessary to end the observation.

CASE 9.—Edward B. (severe typhoid), longshoreman, born in Ireland, 36 years old; admitted October 3, 1914, discharged February, 1915.

*History.*—He remembers no previous illnesses. October 1 he began to suffer from headache, pains all over the body and abdominal cramps, with diarrhea and three to four stools a day. He had no nausea and the appetite was good.

*Physical Examination.*—Well-nourished man of medium frame, fairly muscular. He is dull and apathetic and moderately prostrated. The heart is rapid, not enlarged, the lungs are clear, abdomen soft, spleen palpable. There are a few rose spots.

The blood on October 4 was sterile, but gave a positive Widal test. On the sixth he was very drowsy; by the tenth he was comfortable and eating well. October 13 the temperature had again risen, the pulse rate had jumped to 120 and the quality of the pulse was poor. On the twentieth he was much better and was taking his food well, but the abdomen was slightly distended. By November 1 the temperature was almost normal and the general condition excellent in spite of a small rapid weak pulse. By November 7 the temperature was up again, and he was beginning to feel indisposed. The appetite was poor and the pulse rate between 138 and 148. During the next few days the pulse was very rapid, slightly irregular, and very weak. He was very toxic but was rational except for short periods when the mind was a little hazy. November 16 he had a small hemorrhage with a short period of collapse, but recovered quickly. His condition improved steadily until December 3 when the temper-

ature rose once more and he suffered from a moderately severe relapse, lasting until December 21. Following this was a period of three days of normal temperature and then a fourth relapse, very mild in character lasting only three days. During the whole period of his illness his nutrition remained good; he was always cheerful and read the newspaper almost every day.

CASE 10.—John K. (typhoid fever, mild), deck hand, Polish, aged 35; admitted Dec. 12, 1914, discharged Jan. 27, 1915.

*History.*—December 2, began to suffer from malaise. December 5 had a severe chill and took to bed; since then has had chills almost every day. Has had continuous headache, has vomited frequently and has been constipated.

*Physical Examination.*—Tall and thin, fairly muscular. Tongue dry, coated, fissured. Heart and lungs clear, spleen palpable, many rose spots.

December 12, the blood culture was sterile but the Widal positive. On the thirteenth he had his last chill, on the sixteenth he was apathetic and prostrated, pulse was slow and dicrotic, there was a patch of herpes on the upper lip. As the temperature fell during the next few days his condition improved rapidly, but the apathy remained until the temperature was normal, and he was unusually quiet, remaining almost motionless all day long. Convalescence was rapid.

#### DISCUSSION OF RESULTS

*Law of Conservation of Energy in Fever.*—The law of conservation of energy has been shown to apply to the lower animals, to normal men and to babies, and has been discussed in the previous paper (Paper 6) on normal controls, in which it was demonstrated that with normal men a satisfactory agreement between the direct and indirect calorimetry could be obtained in periods as short as one hour. While there are few who doubt that the law applies to men with fever, it may not be superfluous to bring forward proof.

An agreement of the direct and indirect calorimetry within the limits of experimental error indicates that protein, fat and carbohydrate are oxidized to the same or approximately the same end products as in health and that in the oxidation they give off the standard amounts of heat. The method of calculating the indirect calorimetry depends on the assumption that the calories furnished by each gram of protein, fat and carbohydrate correspond to the standard figures of Loewy,<sup>7</sup> protein 4.32, fat 9.46, starch 4.18. The results obtained by the method of direct calorimetry, which is dependent only on fundamental laws of physics, must remain the standard method of comparison when considering large groups of experiments. Once the agreement has been proved for the group, the method of indirect calorimetry is preferable for individual experiments as has been shown in previous papers on account of the technical difficulty of the method of direct calorimetry in short periods.

Table 1 gives a summary of the percentage divergence of the direct and indirect calorimetry in all the experiments on the typhoid patients,

7. Loewy: *Der respiratorische und der Gesamtumsatz*, Oppenheimer's Handb. der Biochem, 1911, iv, 280.

the great majority of them being three hours long. In all cases the indirect method was used as a standard. If we consider the total measurement of 12,822 calories, we find the direct method, as calculated from the rectal temperature, gives results only 2.2 per cent. lower than the indirect. In almost half of the experiments the body temperature was measured by a thermometer of two units strapped on the thorax in the region of the apex of the heart and just below the right nipple, each unit being covered by a pad of cotton about 15 cm. square and 4 cm. thick. The rectal thermometer was inserted about 12 cm. beyond the sphincter. In a previous paper attention has been called to the fact that in these typhoid cases in which both methods were tried

TABLE 1.—PERCENTAGE DIVERGENCE OF DIRECT FROM INDIRECT CALORIMETRY IN THE INDIVIDUAL EXPERIMENTS

Percentage Divergence	Number of Experiments Falling in Each Group					
	According to Rectal Temperature			According to Surface Temperature		
	+ Divergence	— Divergence	Total	+	—	Total
0-5.....	17	22	39	11	7	18
6-10.....	3	15	18	2	7	9
11-17.....	1	3	4	0	1	1
Total.....	..	..	61	..	..	28
Average Error..	..	..	±4.9%	..	..	±4.0%

	Indirect	Direct*	Divergence
Total calories measured in all experiments.....	12,822.03	12,539.67	—2.2
Excluding first periods.....	8,470.93	8,488.97	+0.2
Calories measured in febrile experiments excluding all first periods.....	5,720.21	5,583.55	—2.4

\* According to rectal temperature.

slightly better results were obtained by using the surface thermometers to give the temperature changes of the body than by using the rectal. In the long run the rectal thermometer is the more reliable, since it is not so easily displaced by bodily movement, but enough evidence has been accumulated to show that the rectal temperature does not always change in the same degree and not always in the same direction as the average body change. As the body cools off there may be a relative increase in the heat near the surface of the body, since this is the place that most of the heat is dissipated. The opposite takes place when the temperature is rising. On account of the rapid circulation of blood

there is, of course, a tendency for the temperature curves of the different parts of the body to follow the deep temperature as measured in the rectum.

In the sixty-one experiments in which the rectal temperature was measured the average divergence of the indirect calorimetry from the direct calorimetry (as based on the rectal temperature) is only  $\pm 4.9$  per cent. In twenty-eight of these experiments it was possible to base the calculations on the changes in the surface temperature, with an average divergence of 4.0 per cent. using this latter method. This divergence of 4 or 5 per cent. is not more than one often finds among normal controls, since the technic is difficult even with trained subjects. The reason for the total minus error of 2.2 per cent. is not clear. The largest part of this error frequently falls in the first hour, especially in patients with fever, and we have been led to suspect that the subject continues to give out heat to the wooden bed frame and to the bedding even after he has been on the bed for an hour. If we excluded from our calculations the first periods, while the calorimeter is still coming into thermal equilibrium, we find that the direct and indirect methods agree within 0.2 per cent. If we consider only those experiments made during the febrile period, we find a larger proportion show a minus error in the direct calorimetry than when we take all the experiments put together. Excluding the first hours of each experiment, however, the direct calorimetry gives a total only 2.4 per cent. lower than the indirect. The difference is so small that it might be found in a group of normal controls. It may be entirely accounted for by the difficulty in measuring the average body temperature during fever.

*Basal Metabolism in Typhoid Fever.*—In Paper 4 of this series the reasons have been given for the selection of the standard of the average normal basal metabolism. The figure of 34.7 calories per square meter per hour as based on Meeh's formula has been used in all the calculations. It was impossible to use the new surface formula as a standard since this was not devised until most of the typhoid work had been completed.

The relationship of the basal metabolism of the typhoid patients in the various stages of the disease to the normal is shown in Table 2. This corresponds in a striking manner with the averages of the fasting typhoid patients investigated by Kraus, Svenson, Grafe and Rolly and collected by us in a previous publication.<sup>1</sup> It is evident from the general trend of the results that the total metabolism increases and falls in a curve roughly parallel with the body temperature, and that the period when it drops below normal in many patients corresponds with the period of subnormal temperature which occurs so often in the first week of convalescence. From a study of the results obtained by the

calorimeter and by various smaller types of respiration apparatus, it is apparent that there is considerable variation in the heat production of different patients and the same patient at different stages of the fever. While we can state that the average increase in typhoid fever is approximately 40 per cent., we must remember that figures over 50 per cent. are frequently encountered. This should make us cautious in drawing too many deductions from feeding experiments unaccompanied by determinations of the respiratory metabolism. It should also be remembered that typhoid fever is the only fever which has been thoroughly investigated and that if variations occur in this one disease the variations may be quite different in other febrile diseases such as erysipelas, pneumonia, puerperal fever, etc.

TABLE 2.—BASAL METABOLISM, ACCORDING TO PERIODS OF TYPHOID FEVER

Periods	Number of Patients	Number of Observations	Average Per Cent. Rise Above Average Normal 34.7 Cal. per Sq. M.	Average Respiratory Quotient
Ascending temperature .....	2	2	+37	0.79
Continued temperature .....	5	7	+42	0.77
Early steep curve.....	3	4	+26	0.82
Late steep curve.....	3	3	+16	0.82
Relapse—				
Ascending temperature .....	2	3	+26	0.82
Continued temperature .....	2	2	+51	0.76
Early steep curve.....	2	4	+36	0.78
Late steep curve.....	1	1	+16	0.79
Convalescence—				
First week .....	3	4	— 2	0.91
Second week .....	3	5	+ 6	0.88
Third week .....	1	1	+17	0.81
Fourth week .....	2	2	+15	0.86
Fifth week .....	2	2	+ 4	0.81

Benedict and his co-workers in all their recent publications have drawn attention to the fact that pulse rate and total metabolism show curves which are roughly parallel. As might be expected this parallelism is not as apparent in typhoid fever as in the conditions they have studied. Typhoid is characterized by a slow pulse in the first two weeks when the metabolism is high. The experiments here reported do not show any striking agreement in the rise and fall of the two curves.

*The Specific Dynamic Action of Food.*—When studying the effects of the high calory diet in typhoid fever with the small Benedict respira-

tion apparatus, the writers noted the fact that the metabolism of liberally fed typhoid patients was scarcely raised above the metabolism of fasting typhoid patients. The conclusion was drawn that food exhibits little or no specific dynamic action in typhoid fever. One of the chief objects of the present research was to study this striking phenomenon more closely, inasmuch as some observers, among them Von Noorden,<sup>8</sup> have stated that the specific dynamic action of food was increased in fever, exophthalmic goiter and several other conditions.

We have seldom kept typhoid patients in the calorimeter for periods exceeding three or four hours. After this length of time the patients often become restless and bored, making the results unreliable. This

TABLE 3.—SPECIFIC DYNAMIC ACTION OF PROTEIN AND CARBOHYDRATE IN HEALTH, FEVER AND CONVALESCENCE

Subjects	Number of Experiments	Average Gm. of Nitrogen or Glucose in Food	Average Gm. Food per Kg. Body Weight Nitrogen or Glucose	Average Per Cent. Rise in Metabolism
<b>Protein meal</b>				
Two normal men.....	2	10.1	0.147	9.3
Four febrile patients.....	6	8.6	0.174	4.5
Four convalescents .....	5	10.2	0.217	16.6
<b>Commercial glucose</b>				
Three normal men.....	3	115.0	1.6	9.1
Two febrile patients.....	4	115.0	2.2	1.0
Three convalescents .....	3	115.0	2.7	9.8

\* Since the completion of Paper 4 two more normal controls have been given the test meals. Morris S. on Dec. 18, 1914, showed a rise of 6.5 per cent. after a meal containing 9.6 gm. N.; Albert G. on Jan. 6, 1915, showed an increase of 9.0 per cent. in his metabolism after 115 gm. commercial glucose.

has made it impossible to determine the basal metabolism in a two hour experiment and follow it immediately by a three or four hour experiment to find out the effect of food. Moreover, in such a long period the temperature might change several degrees, making the results difficult of interpretation. In the case of normal controls, the basal metabolism is so uniform from day to day that very accurate results can be obtained by determining the basal metabolism and the metabolism after food on different days. In fever the change in the level of metabolism from day to day makes the results less accurate but the error will be small if certain precautions are taken. The level of basal heat production changes in a fairly gradual and uniform curve and

8. Von Noorden: *New Aspects of Diabetes*, New York, E. B. Treat & Co., 1912, p. 20.



there is but a small change in twenty-four hours unless the temperature or the general condition of the patient changes markedly. For this reason the effect of a given meal has been determined sometimes the day before, sometimes the day after and sometimes the day between basal experiments. The protein meal was given six times in the febrile period and the glucose meal four times. It is against the laws of probability that the basal metabolism should take a sudden change in the same direction on all these days.

The fact that the average amount of protein given in the febrile period was less than that given in health was due to the poor appetite of the patients at the height of the disease. Even in health and in

TABLE 4.—CHART SHOWING NEGATIVE NITROGEN BALANCES IN TYPHOID PATIENTS WHO RECEIVE FOOD CALORIES IN EXCESS OF CALCULATED HEAT PRODUCTION

Patient	Dates or Days of Disease Inclusive	Days in Period	Range of Maximum Temperature, Degrees F.	Calculated Heat Production, Cal.*	Food Calories*	Food N, Gm.*	Nitrogen Balance Gm.*
Morris S.	Oct. 23-Nov. 3	12	102.8-104.6	2,266	2,863	16.4	-4.4
	Dec. 19-24	6	101.9-105.1	2,085	2,989	13.2	-2.4
Charles F.	Nov. 28-30	3	101.2-103.4	1,752	2,458	12.0	-4.6
Karl S. ...	Jan. 12-18	7	101.0-105.0	2,197	2,985	16.1	-3.2
	Jan. 19-22	4	98.8- 99.0	1,678	2,819	14.6	-1.9
John K....	Jan. 15-20	6	103.2-104.0	2,568			
Frank W.†	Days of Disease 11-14	4	104.0-105.4	2,200	2,250	11.3	-5.0
	15-19	5	103.0-104.0	2,238	3,320	15.3	-3.3
	20-23	4	101.0-103.6	2,054	2,362	15.9	-1.6

\* Figures given are averages for twenty-four hours.

† Taken from Coleman and Du Bois.<sup>1</sup>

convalescence the meal is a large one, containing almost as much protein as most people consume in a day. We must remember also that the normal controls weighed 75 and 63 kg. when they took this meal and that the typhoid patients weighed 51, 58, 35, and 54 kg., respectively. As is shown in Table 3 the controls received less nitrogen per unit of body weight than the fever patients. We can therefore state that protein and glucose exhibit a much smaller specific dynamic action in typhoid fever than in health, while in convalescence from the disease the specific dynamic action seems to be greater than normal. In the case of glucose there was practically no specific dynamic action in fever, and in the case of Morris S. the specific dynamic action of the protein was very slight.

The cause for this phenomenon has not yet been definitely ascertained but the most plausible theory was stated by Dr. Graham Lusk<sup>9</sup> in the discussion on the symposium on nutrition at Atlantic City in 1914. He called attention to the well known fact that if the metabolism be increased by lowering the environmental temperature there may be

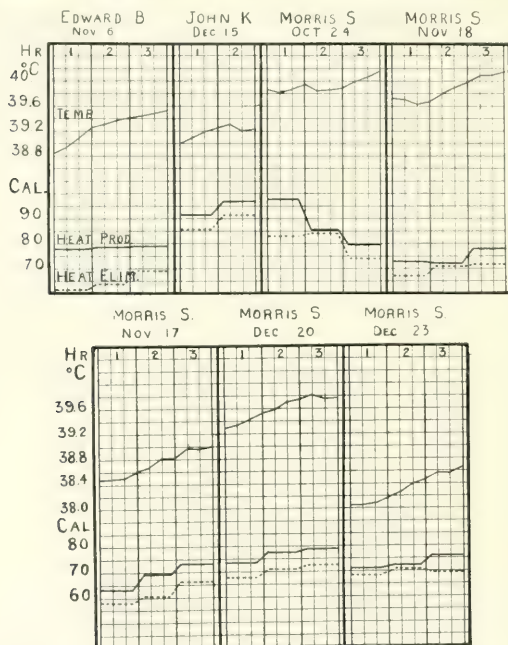


Chart 1.—Curves showing the relationship of heat production and heat elimination in fever. Rising temperature. The uppermost line shows the rectal temperature as measured every twenty minutes. The heavy continued line represents the heat production in hourly periods as determined by the method of indirect calorimetry. The dotted line gives the heat elimination as determined by the measurement of the calories of radiation, conduction and vaporization. The difference between the levels of these two lines represents the heat stored in the body as the temperature rises. Note the fact that in every case except one the heat elimination increases with a rising temperature.

no specific dynamic action as usually induced by ingested food. In like manner if the metabolism be raised in fever, food ingestion may cause no increase. He also stated that since protein metabolism in fever

9. Lusk: Jour. Am. Med. Assn., 1914, lxiii, 831, foot of page.

can never be reduced to as low a level as is present in the normal organism, therefore protein ingestion in fever often merely serves to replace the protein already breaking up in increased quantity, and such protein ingestion would not then serve to increase the heat production.

*The Regulation of Body Temperature.*—The study of the regulation of body temperature is one that demands the utmost accuracy of technic. The question at issue is whether a rise in temperature is due to an increase in heat production or a decrease in heat elimination. Previous investigators have tried to solve this problem on data obtained from the direct calorimetry alone, or from the indirect calorimetry accompanied by measurements of body temperature. In either of these two methods the whole calculation would depend on the exact

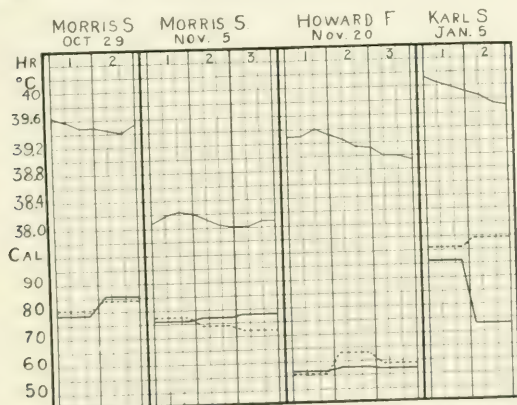


Chart 2.—Curves showing the relationship of heat production and heat elimination in fever. (See legend Chart 1.) Temperature level or falling. In the last two experiments it will be noted that the heat elimination rises above the production.

measurement of the average change in body temperature, the exact calculation of specific heat of the body and the amount of heat stored in or lost from the body. It has been shown in this and preceding papers that these measurements and calculations are the weakest points in the science of calorimetry and it is only very recently that the technic has been so developed that investigators have attempted a comparison of the methods of direct and indirect calorimetry in periods shorter than six to twelve hours, periods obviously too long for the study of the problem in question. If, in a period of experimentation, the results obtained by the method of indirect calorimetry and by the method of

direct calorimetry, using either the rectal or the surface temperature, do not agree within 5 per cent., we must suspect some error, probably in the measurement of the average body temperature change. For this reason we have eliminated from the discussion all experiments in which the two methods do not agree within 5 per cent. It is also preferable to eliminate all experiments after the taking of food and all experiments in which the subject was not quiet. This gives us eleven experiments during the febrile period in which the technic left nothing to be desired.

In Chart 1 are grouped those experiments in which there was a rising body temperature. The dotted line shows the total heat eliminated from the body by means of radiation, conduction and vaporization. The continued line shows the heat production as determined by the method of indirect calorimetry, which does not use a single factor that affects the dotted line. With a rising body temperature the heat production within the body must be greater than the elimination to provide for the storage of heat in the tissues. Many are of the opinion that the rise in temperature is chiefly due to a decrease in the heat elimination. This we find to be the case only in the last hour of one of the seven observations, there being a sharp drop in both heat production and elimination towards the end of the experiment on Morris S. on October 24. In all the other periods the rising temperature was accompanied by an increasing heat production which outweighed the increasing heat elimination.

In Chart 2 which shows periods in which the body temperatures were fairly level the production and elimination were about equal and constant. In the two observations with falling temperature the heat production remained fairly level while the elimination was increased.

*Heat Production, Weight and Nitrogen Equilibrium.*—In the cases here studied it is possible to make a comparison of the caloric intake and the caloric output. The intake consists of the calories of the food. The output is made up of many factors, but principally of calories lost by radiation, conduction and the evaporation of water. The first and most important consideration is the determination of the basal heat production as measured by the methods of direct and indirect calorimetry. As has been shown above, the two methods agree within 2 per cent. The actual heat production during the different hours of the day can depart from the basal as a result of various factors. We have shown above that the ingestion of large amounts of food causes but a slight increase in metabolism, averaging less than 5 per cent. in the case of protein and only 1 per cent. in the case of carbohydrate. These increases may be considered the maxima since the amounts of foods given were the largest the patient could take and the hours of the

observation were the hours of the greatest specific dynamic action. The exact percentage rise caused by the stimulation of the food taken during the whole day is problematical but may be estimated as about 3 per cent. The percentage of calories lost in the feces has been studied in two previous papers and has been found to be practically normal. The calories lost as urea and in the feces are taken into consideration in the calculation of the fuel values of the food. In the one case in which there was alimentary glycosuria (Frank W.),<sup>1</sup> the calories lost as dextrose have been subtracted from the intake. In a previous paper the writers have discussed the evidence against an abnormal loss of partially oxidized carbon compounds in the urine and have come to the conclusion that this factor is negligible. The entire absence of abnormal respiratory quotients supports this view. The lowest quotient found was 0.72, the highest 1.04, obtained respectively during fasting and high carbohydrate ingestion, and thus exhibiting entirely normal relations.

The most uncertain factor is the variation in heat production caused by changes in the muscular activity. It is quite possible that a patient who is very delirious and very restless might produce twice as many calories as when quiet. The total heat production of such patients could be determined only by the Middletown type of experiment in which the subject was kept in a respiration calorimeter for days at a time. Such experiments are obviously impossible in typhoid fever. The question remains as to whether we obtain a fair sample of the day's metabolism by making two or three observations a week between the hours of 11 in the morning and 2 or 3 o'clock in the afternoon. This period includes some of the morning hours when the metabolism is said to be low and some of the afternoon hours when it is said to be high. During the experiment the activity of the patient has been almost the same as the activity observed in the ward during the greater part of the day between the hours of 5 in the morning and 8 in the evening. In the calorimeter the subjects are allowed to turn from side to side several times during the hour and they shift their position often enough to make themselves comfortable, which is exactly what they do in their beds in the ward. Part of the time they doze and part of the time they are awake and are looking out of the calorimeter window. In the ward they are kept flat in bed and are never allowed to sit up until the temperature has been normal for several days. They are never given cold tubs and hardly ever given cold sponges. Their food is served on trays and they help themselves with a minimum of exertion. In the morning the nurse gives each patient an enema, sponges

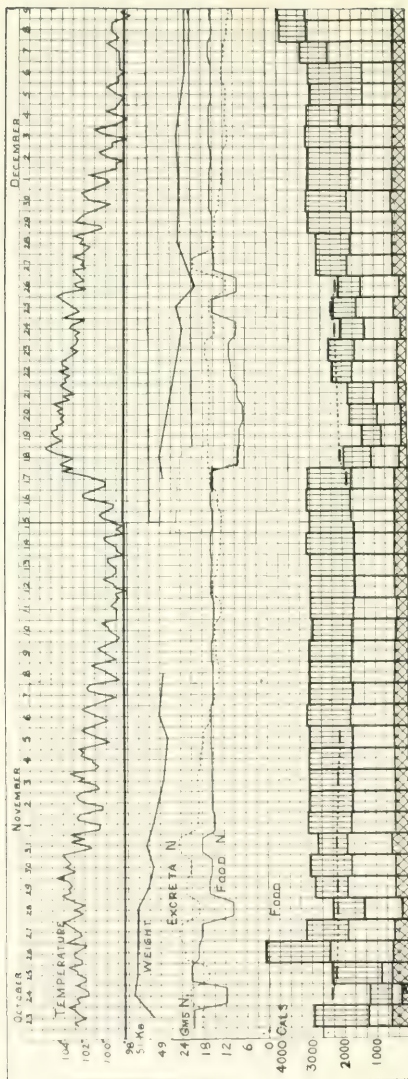


Chart 3.—Part 1



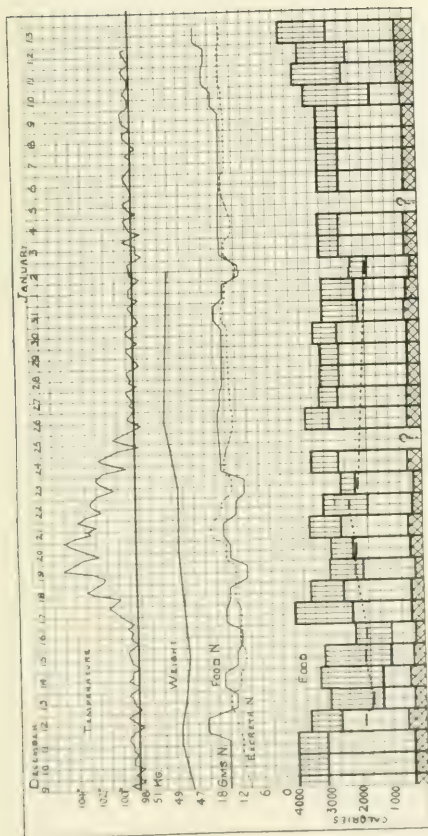


Chart 3.—Part 2

Chart 3. Morris S.—Temperature, body weight, Food nitrogen, continuous line; excreta nitrogen, dotted line. At the base of the chart, columns representing total calories of food. Protein calories, crossed diagonals—fat calories, blank—carbohydrate calories, vertical lines. The dot-dash line represents the estimated heat production in calories for twenty-four hours. The dashes are placed on days of the observations in the calorimeter. Note that the calories of the food exceed the estimated heat production except for a period during the first relapse. Food was not measured on December 25th and January 5th.

him off with warm water, slides him from his bed to the weighing platform, makes up his bed and slides him back again. During the rest of the day he is seldom disturbed and he spends his time dozing, reading or talking with his neighbors. A few of the patients have been mildly irrational for a few days at a time and such occurrences have been noted in detail in the histories. *Subsultus tendinum* and *jactitation* have rarely been observed. On the other hand, there must be a reduction of the metabolism at night since the patients sleep soundly and are seldom disturbed. In a previous paper we have estimated that the bodily activity increases the metabolism during the whole day to an average of 10 per cent. above its basal metabolism. Since that time we have had the opportunity of making two observations on patients who were irrational and restless. November 3 Morris S. was in the calorimeter for three hours. During the first hour he was unusually quiet, during the second hour he was restless and tossed about the bed, during the third hour he was evidently irrational, tossed about and wrote three or four long notes which he held up to the calorimeter window to tell us about the animals that were biting him with their sharp teeth.

In spite of this unusual activity his metabolism during the three hour period was only 43 per cent. above the normal and was only 5 per cent. higher than during the quiet basal observation made two days later, when the temperature was lower. Edward B. on Nov. 10, 1914, was in the calorimeter with a temperature of 40.3 C., and during the second and third hours was restless and mildly irrational. His heat production was only 51 per cent. above the average normal. These two observations, which are fair samples of the severest symptoms observed in the typhoid patients presented in this paper, do not indicate any unusual degree of increase of heat production from the moderate activity. There may be an uneconomical expenditure of energy in typhoid in the performance of a certain task but even so the total expenditure is not great in these cases. It is hoped that at a later date the question of muscular efficiency in fever may be solved by having typhoid patients and normal controls do a stated amount of work on an ergometer while in the calorimeter.

A detailed consideration of all the factors is of importance when one attempts to draw conclusions from a discrepancy between the calculated intake and the calculated output. It is necessary to consider the possible errors in the various determinations and it is necessary to select somewhat arbitrary average percentages for the various factors. The measurement of the food intake is unusually accurate. Most of

the foods such as cereals, bread, sugars, egg white and egg yolk, butter and crackers vary but slightly from the samples analyzed. The other foods given, such as milk, cream, and dried apples are not subject to large enough variations to affect the results. Foods subject to significant variations are carefully avoided.

The methods of preparation and weighing have been described in another paper and they are believed to be accurate within 2 per cent. It is doubtful if this error combined with the error in the variation of the individual foods exceeds plus or minus 5 per cent. and there is no factor to throw the error on one side of the scale more often than on the other. The heat production of the patients as determined by the method of indirect calorimetry is not subject to an error of more than 1 or 2 per cent. on the average, although it is possible that some individual observations may show an error of 5 per cent. The collection of the twenty-four hour specimens of urine and the estimation of

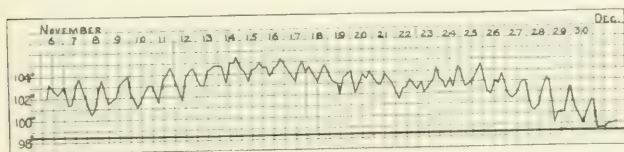


Chart 4.—Charles F. Temperature curve.

the nitrogen are so carefully controlled by duplicate analyses and checks in the collection of specimens and in the calculations that there is no chance for an error greater than 1 per cent. In the cases in which the feces were not analyzed the method of estimating the feces nitrogen as 10 per cent. of the food nitrogen gives a plus or minus error of less than half a gram a day while there is possibly as great an error in the fact that we do not take into account the nitrogen losses through the skin.

In order to estimate the caloric output of typhoid patients on whom respiration experiments were made, one can add to the basal metabolism on average 3 per cent. for the specific dynamic action of the food and 10 per cent. for muscular activity. We can, therefore, calculate with reasonable accuracy the heat production for the day by adding 13 per cent. to the figures obtained in the febrile basal experiments and 10 per cent. to the figures obtained in the experiments after food. In the cases in which several observations were made it seems fair to plot a smooth curve and consider that the heat production of the non-experi-

mental days was the same as on the days in which actual determinations were made.

If we look now at Table 4 and Charts (3), (6) and (8), it becomes evident that three of the patients reported in this paper and one reported in a previous paper<sup>1</sup> showed a distinct negative nitrogen balance when they were receiving considerably more calories than were sufficient to cover the calculated heat production. A glance at the food charts will show that the typhoid patients were given 12 to 16 grams of nitrogen a day and that the proportions of fat and carbohydrate were well balanced. The only criticism of the manner of feeding is that on the days of the basal determinations it was necessary for the patient to fast sixteen to twenty hours. One might expect a slight negative nitrogen balance at such times, but this should be offset by a positive balance the next day. As a matter of fact the negative balance is not much greater on the experi-

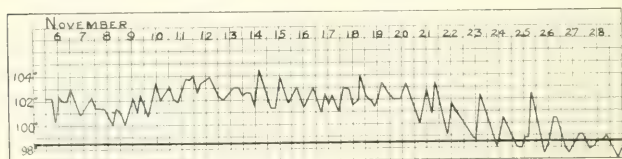


Chart 5.—Howard F. Temperature curve.

mental days. Moreover, as was pointed out in the previous paper, many patients who have not been the subject of respiration experiments have shown a persistent negative nitrogen balance on a diet much greater than the estimated heat production and have not come into nitrogen equilibrium until the theoretical requirement was exceeded by from 50 to 110 per cent.

In another place<sup>1</sup> when touching on this subject we referred to the possibility of a storage of fat while there was a negative nitrogen balance and loss of body weight. The body weight is notoriously a poor index of gain or loss of body tissue except in long periods of observation. The body changes its content of water so easily and so rapidly with changing diets and changing periods of the disease that it would be very easy to store 1 or 2 kilograms of fat without noticeable effect on the weight. We must remember that 1 kilogram of fat represents about 9,300 calories. Even without assuming a change in the water concentration of the body, it is possible to account for the storage of the excess calories. In the tables one can find several periods of almost con-

stant body weight when the patient was losing nitrogen. If we consider that for every 3 grams of nitrogen lost the patient loses about 100 grams of muscle tissue, it is possible to calculate the total muscle tissue lost. If this were replaced by fat the weight would remain constant and the storage of the excess calories could easily be accounted for. For example, Morris S. between October 23 and November 3 lost about 1,770 grams of muscle tissue, which could be replaced by enough fat to represent 15,900 calories.

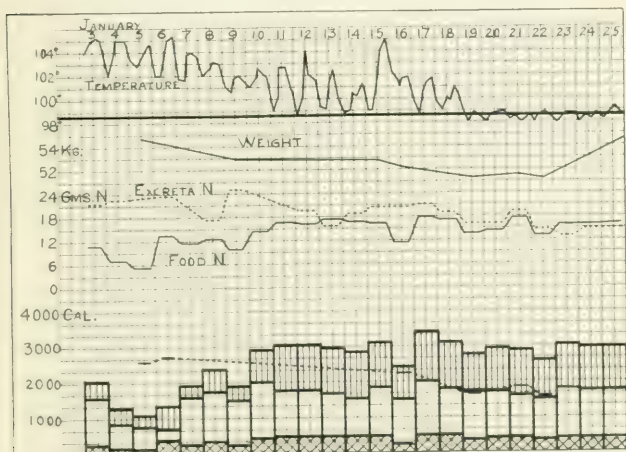


Chart 6.—Karl S. Temperature and body weight. Food nitrogen, continuous line; excreta nitrogen, dotted line. The columns at base represent calories in food. Protein calories crossed diagonals, fat calories blank, carbohydrate calories vertical lines. Dot-dash line represents the estimated heat production in calories for twenty-four hours, dashes being placed on the days of the calorimeter observations. Note the negative balance during the last days of the fever when the patient was receiving in food more calories than the estimated heat production.

In none of the cases were the protein and carbohydrate calories together sufficient to cover the heat production, so it is not necessary to assume the transformation of carbohydrate into fat, although we have shown that this is possible during fever in one patient<sup>1</sup> (Salvatore L.).

*The Toxic Destruction of Protein.*—The proof of the fact that typhoid patients show a negative nitrogen balance on a diet which furnishes more calories than the heat production, is perhaps the most



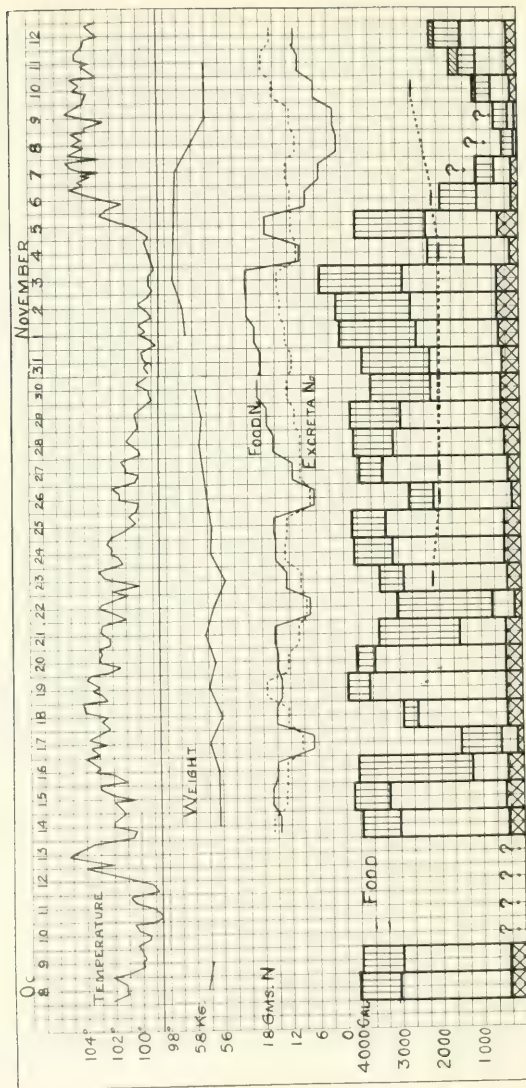


Chart 7—Edward B. Temperature, body weight, food and excreta nitrogen. Food calories and dot-dash line representing estimated heat production. On November 7th, 8th and 9th, patient vomited, making measurement of food intake somewhat inaccurate. November 10th, 11th and 12th he received some alcohol calories.



important piece of evidence which has yet been presented in the discussion of the so-called toxic destruction of protein. Clinicians have long been aware of the large excretion of nitrogen in fever and have attributed it to an abnormal destruction of protein caused by the toxins of the disease. It is not necessary in this connection to review the older clinical work, since that is admirably presented in the standard discus-

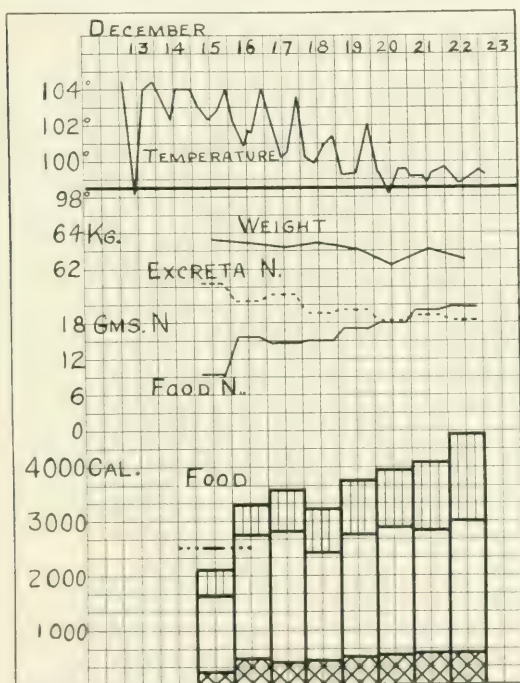


Chart 8.—John K. Temperature, body weight, food and excreta nitrogen. Food calories and dot-dash line showing estimated heat production.

sions of metabolism in fever. The results of the large number of investigations made on lower animals, while important, cannot with certainty be transferred to man.

The question of the toxic destruction of protein took on a new aspect when in 1909 Shaffer and Coleman<sup>8</sup> showed that it was possible

to obtain nitrogen balance in typhoid patients, even during the second and third weeks of the disease. This they accomplished only by making the total caloric value of the food very high, from 60 to 90 calories per kilogram, and the food nitrogen from 9 to 15 grams. In their discussion of the results they expressed the opinion that "...it is perhaps improbable that the total heat production reached the values represented by the larger amounts of food." This work proved that there was no toxic destruction in the sense of a nitrogen loss which could not be counterbalanced by the nitrogen intake.

The question of the average heat production of typhoid patients was fully discussed in last year's paper<sup>1</sup> and attention was drawn to the fact that typhoid patients did not come into nitrogen equilibrium until their theoretical caloric requirement was exceeded by from 50 to 110 per cent. Grafe<sup>10</sup> in 1911 had shown that his typhoid patients when studied in a respiration chamber, ten to sixteen hours after their last meal, derived about 10 to 20 per cent. of their calories from protein, a percentage usually found in normal men. From this Grafe concluded that he had shown that the protein metabolism in fever was not abnormal. The percentage of calories derived from protein on the first eighteen hours after food ingestion depends largely on the previous level of the protein metabolism. Normal individuals who have been taking 15 to 19 grams of nitrogen a day will naturally derive about 15 to 20 per cent. of their calories from protein as is shown in Paper 4 of this series. Normal individuals who have been maintaining themselves in nitrogen balance on 4 to 5 grams a day will derive only 5 per cent. of their calories from protein. The comparison should have been made between normal men and typhoid patients while both were on their nitrogen minima. This will be shown later in a discussion of Kocher's work.

Rolland<sup>11</sup> working under Grafe's direction brought several fever patients into nitrogen balance by means of a caloric intake which she believed to be equal to the heat production as estimated from the averages of other patients. Respiration experiments were not made on the patients themselves. Our reasons for believing that the food intake was above the requirement have been set forth in another place<sup>1</sup> (p. 38).

Recent work from Friedrich Müller's clinic has thrown important light on the subject. Graham and Poulton<sup>12</sup> established themselves

10. Grafe E.: Untersuchungen über den Stoff- und Kraftwechsel im Fieber, *Deutsch. Arch. f. klin. Med.*, 1911, ci, 209.

11. Rolland, Anne: Zur Frage des toxischen Eiweisszerfalls im Fieber des Menschen, *Deutsch. Arch. f. klin. Med.*, 1912, cvii, 440.

12. Graham and Poulton: Influence of Temperature on Protein Metabolism, *Quart. Jour. Med.*, 1912, vi, 82.

on a minimal nitrogen elimination of 4 to 5 grams a day and found no increase in the elimination when they raised their temperatures to about 40 C. by means of a steam bath. Kocher<sup>13</sup> in two normal subjects established a nitrogen minimum at a similar level and found no increase when he raised the heat production by means of a 60 kilometer walk. All of these experiments were made on a caloric intake calculated to cover the requirement. They indicate that rise in temperature alone or increase in heat production alone will not cause an increased protein metabolism, at least when applied for a portion of one day. Kocher then attempted by means of a diet amply sufficient to cover the calculated requirement to bring down the nitrogen elimination of fever patients to the low level obtained in normal men. This he found to be impossible until the active stage of the disease was passed. Grafe<sup>14</sup> in a recent paper has criticized these experiments.

To all of the patients in Table 4 food was given which had an energy content much greater than the amount required by the patients as measured directly when they were in the calorimeter. Although the protein content of the diet, as represented by an intake of 15 grams of nitrogen, was ample to establish nitrogen equilibrium had the diet been given to normal men, it did not accomplish this in typhoid fever. It is difficult to see in this anything except the proof that there is an abnormal destruction of protein in typhoid fever. In some cases the protein destruction continued several days after the temperature had reached a low level. It is impossible to escape the conclusion that the destruction of protein is caused by the toxins of the disease.

#### SUMMARY AND CONCLUSIONS

The heat production of typhoid patients has been measured by the methods of direct and indirect calorimetry in a series of sixty-one experiments. The two methods agreed closely, the total divergence being 2.2 per cent. and the average divergence in the individual experiments being 5 per cent. This and the entire absence of abnormal respiratory quotients indicate that in typhoid fever protein, fat and carbohydrate are oxidized to the same or approximately the same end products as in health, and in their oxidation give off the standard

13. Kocher, Rudolph A.: Ueber die Grosse des Eiweisszerfalls bei Fieber und bei Arbeitsleistung, *Deutsch. Arch. f. klin. Med.*, 1914, cxv, 82.

14. Grafe, E.: Zur Genese des Eiweisszerfalls im Fieber, *Deutsch. Arch. f. klin. Med.*, 1914, cvi, 328.

TABLE 5.—CLINICAL—

Subject Date Weight	Period	End of Period	Carbon- dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.	Direct Calo- rimetry (Rectal Temp.) Cal.	Rectal Temp. C.
Morris S. .... Oct. 24, '13 51.50 kg.	Prelim.	11:35	.....	.....	..	.....	.....	.....	.....	.....	39.80
	1	12:35	30.06	30.02	.73	47.84	0.713	97.69	83.41	84.28	39.95
	2	1:35	27.82	26.13	.77	46.72	0.713	85.89	84.68	81.00	39.89
	3	2:35	26.20	24.04	.70	39.48	0.713	79.28	74.63	85.72	40.17
Morris S. .... Oct. 25, '13 51.22 kg.	Prelim.	11:00	.....	.....	..	.....	.....	.....	.....	.....	39.21
	1	12:00	29.65	26.82	.80	42.10	0.671	88.95	78.03	90.06	39.49
	2	1:00	28.63	25.87	.81	39.10	0.671	85.77	80.11	88.09	39.69
	3	2:00	31.75	25.46	.91	42.82	0.671	86.62	90.07	78.55	39.49
Morris S. .... Oct. 28, '13 51.50 kg.	Prelim.	11:10	.....	.....	..	.....	.....	.....	.....	.....	39.62
	1	12:10	34.12	28.35	.88	43.31	0.732	95.71	92.00	75.53	39.27
	2	1:10	32.64	24.82	.96	42.41	0.732	85.31	94.67	76.33	38.87
	3	2:10	30.25	22.89	.96	39.40	0.732	78.60	86.73	84.65	38.81
	4	3:10	29.93	24.33	.90	34.39	0.732	82.34	78.47	93.97	39.20
	5	4:10	28.38	22.05	.94	31.75	0.732	74.59	74.35	90.84	39.65
Morris S. .... Oct. 29, '13 49.86 kg.	Prelim.	11:10	.....	.....	..	.....	.....	.....	.....	.....	39.63
	1	12:10	26.75	23.77	.82	33.11	0.658	79.00	81.19	76.49	39.50
	2	1:10	27.49	25.95	.77	34.03	0.658	85.28	81.48	85.73	39.54
Morris S. .... Oct. 31, '13 50.28 kg.	Prelim.	11:00	.....	.....	..	.....	.....	.....	.....	.....	39.06
	1	12:00	28.95	25.45	.83	32.13	1.058	84.11	74.09	58.27	38.94
	2	1:00	29.69	24.17	.89	36.41	1.058	81.15	79.19	79.96	39.08
	3	2:00	29.57	26.58	.80	36.76	1.058	87.50	77.70	87.13	39.43
Morris S. .... Nov. 3, '13 48.53 kg.	Prelim.	10:30	.....	.....	..	.....	.....	.....	.....	.....	38.63
	1	11:30	24.91	20.42	.89	28.58	0.499	69.20	56.44	72.99	39.05
	2	12:30	28.70	26.23	.80	33.10	0.499	83.77	74.39	77.80	39.15
	3	1:30	27.53	27.90	.72	42.11	0.499	90.92	86.25	71.74	38.81
Morris S. .... Nov. 5, '13 48.45 kg.	Prelim.	11:20	.....	.....	..	.....	.....	.....	.....	.....	38.08
	1	12:20	25.42	23.10	.80	29.99	0.491	76.70	77.98	81.34	38.19
	2	1:20	26.42	23.05	.83	38.62	0.491	77.19	74.75	67.00	38.01
	3	2:20	25.60	23.65	.79	39.13	0.491	78.29	72.89	75.34	38.10
Morris S. .... Nov. 17, '13 47.99 kg.	Prelim.	11:10	.....	.....	..	.....	.....	.....	.....	.....	38.48
	1	12:10	21.90	19.01	.84	24.39	0.336	63.87	57.98	62.77	38.61
	2	1:10	23.58	20.82	.82	24.44	0.336	69.76	60.70	69.71	38.82
	3	2:10	23.79	22.28	.78	26.06	0.336	73.79	66.08	72.85	39.00
Morris S. .... Nov. 18, '13 48.77 kg.	Prelim.	11:00	.....	.....	..	.....	.....	.....	.....	.....	39.72
	1	12:00	24.40	22.01	.81	26.55	0.567	73.01	67.36	64.94	39.67
	2	1:00	26.37	21.38	.90	28.15	0.567	72.56	71.65	82.60	39.98
	3	2:00	25.91	23.57	.80	28.88	0.567	78.11	72.05	77.47	40.15
Morris S. .... Nov. 24, '13 46.69 kg.	Prelim.	11:13	.....	.....	..	.....	.....	.....	.....	.....	39.54
	1	12:13	29.17	25.27	.78	29.24	0.514	83.56	67.50	68.12	39.59
	2	1:13	26.91	24.54	.75	32.68	0.514	85.26	75.16	64.72	39.33
	3	2:13	26.41	25.48	.75	35.00	0.514	83.64	80.48	73.52	39.16

# —CALORIMETRY IN TYPHOID FEVER

Surface Temp., C.	Average Pulse	Work Added., Cm.	Non-Protein. R. Q.	Per Cent. Calories from			Calories Per Hour		Remarks
				Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M.	
.....	96(?)	36.0	.71	24	55	1	1.90	57.33	Basal.
.....	96	21.0	.77	28	58	14	1.67	50.40	
.....	105	17.0	.79	31	49	20	1.54	46.53	
.....	101	30.0+	.80	20	54	26	1.74	52.36	9:30-10:00 a. m., protein meal. 9.0 gm. N.
.....	96	21.5	.81	21	52	27	1.68	50.48	
.....	105	18.0++	.94	21	17	62	1.69	50.98	
.....	119	35.0	.90	20	29	51	1.88	66.70	At 10:22, 115 gm. com. glucose = 100 gm. dextrose. Asleep from 3:3:40.
.....	113	25.0+5?	1.01	23	..	77	1.68	50.54	
.....	108	30.5	1.02	25	..	75	1.55	46.56	
.....	108	18.0	.93	24	19	57	1.62	48.78	
.....	107	9.0	.99	26	3	71	1.47	44.19	
.....	105	24.0	.82	22	47	31	1.58	47.17	Basal.
.....	106	17.5	.76	20	65	15	1.70	50.91	
.....	101	10.0 (?)	.84	33	36	31	1.68	50.16	8:40-9:20, protein meal: 10.3 gm. N.
.....	102	11.2+	.95	35	12	53	1.62	48.39	
.....	98	9.5	.81	32	44	24	1.74	52.18	
.....	106	11.7	.91	19	25	56	1.42	42.09	Basal. 1st. hr. quiet, 2d. hr. restless, 3d. hr. restless; wrote 3 or 4 notes.
.....	111	32.0	.79	16	59	25	1.71	50.96	
.....	106	8.0+	.70	15	85	..	1.86	55.30	
.....	98	9.5	.80	17	56	27	1.58	46.89	Basal.
.....	102	8.0	.84	17	45	38	1.59	47.18	
.....	112	8.0	.78	17	61	22	1.62	47.86	
27.29									
27.52	100	11.6	.84	14	45	41	1.33	39.28	Basal.
27.83	112	6.8	.83	13	51	36	1.45	42.90	
27.94	112	3.9	.77	12	68	20	1.54	45.38	
28.89									
28.98	114	0.3	.81	11	53	27	1.50	44.44	Basal.
29.27	117	14.7	.92	21	50	29	1.49	44.16	
29.19	104	13.7	.80	19	55	26	1.60	47.54	
.....		12.0	.78	16	64	20	1.77	52.32	Basal.
.....	102	0.0	.74	16	70	11	1.81	53.39	
.....	126	0.5	.74	16	72	11	1.78	52.37	

TABLE 5.—CLINICAL CALORIMETRY—

Subject Date Weight	Period	End of Period	Carbon- dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.	Direct Calo- rimetry (Rectal Temp.) Cal.	Rectal Temp. C.
Morris S. .... Nov. 25, '13 47.24 kg.	Prelim.	11:20	.....	.....	..	.....	.....	.....	.....	.....	39.40
	1	12:20	28.17	24.45	.84	29.86	0.618	81.79	71.86	66.66	39.30
	2	1:20	30.38	26.92	.82	47.61	0.618	89.78	91.51	78.22	38.97
	3	2:20	29.26	27.94	.78	48.78	0.618	89.93	88.95	95.35	39.13
Morris S. .... Nov. 26, '13 46.11 kg.	Prelim.	10:50	.....	.....	..	.....	.....	.....	.....	.....	39.61
	1	11:50	26.29	24.80	.77	27.88	0.329	82.10	69.08	52.60	39.19
	2	12:50	25.68	24.64	.76	34.79	0.329	81.28	79.19	71.14	38.99
	3	1:50	25.70	24.85	.75	42.13	0.329	81.84	88.38	79.59	38.77
Morris S. .... Dec. 12, '13 48.61 kg.	Prelim.	10:56	.....	.....	..	.....	.....	.....	.....	.....	37.01
	1	11:56	23.45	20.22	.84	18.48	0.272	68.20	61.73	53.71	36.82
	2	12:56	23.88	20.96	.83	21.26	0.272	70.44	64.58	69.48	36.95
	3	1:56	24.99	21.42	.85	24.01	0.272	72.36	66.64	69.52	37.03
Morris S. .... Dec. 13, '13 48.07 kg.	Prelim.	10:36	.....	.....	..	.....	.....	.....	.....	.....	37.07
	1	11:36	18.99	16.89	.82	18.84	0.323	56.39	58.07	50.93	36.90
	2	12:36	20.10	17.29	.85	19.31	0.323	58.16	58.63	63.06	37.02
	3	1:36	20.76	18.90	.80	20.26	0.323	62.88	61.95	63.59	37.07
Morris S. .... Dec. 15, '13 48.17 kg.	Prelim.	10:52	.....	.....	..	.....	.....	.....	.....	.....	37.30
	1	11:52	24.51	18.29	.98	18.41	0.384	63.45	58.74	47.60	37.03
	2	12:52	26.76	18.98	1.03	20.90	0.384	66.42	63.52	64.97	37.10
	3	1:52	26.83	18.82	1.04	22.07	0.384	65.97	64.19	67.97	37.23
Morris S. .... Dec. 16, '13 47.86 kg.	Prelim.	11:06	.....	.....	..	.....	.....	.....	.....	.....	37.32
	1	12:06	22.51	17.81	.92	20.83	0.299	61.10	63.36	61.62	37.30
	2	1:06	21.91	18.33	.87	21.42	0.299	62.12	62.76	63.36	37.33
	3	2:06	22.37	19.33	.84	21.79	0.299	65.08	63.87	60.35	37.25
Morris S. .... Dec. 19, '13 48.74 kg.	Prelim.	11:10	.....	.....	..	.....	.....	.....	.....	.....	39.19
	1	12:10	27.38	21.99	.91	22.55	0.493	74.94	70.40	67.95	39.14
	2	1:10	30.04	22.70	.96	25.64	0.493	78.51	75.00	84.00	39.41
	3	2:10	29.47	23.51	.91	27.26	0.493	80.32	74.21	87.13	39.75
Morris S. .... Dec. 20, '13 48.52 kg.	Prelim.	10:40	.....	.....	..	.....	.....	.....	.....	.....	39.29
	1	11:40	23.69	22.51	.77	23.81	0.547	73.93	67.11	76.36	39.53
	2	12:40	25.60	23.42	.80	25.60	0.547	77.57	70.95	78.45	39.76
	3	1:40	25.51	23.84	.78	27.47	0.547	78.68	72.88	72.56	39.77
Morris S. .... Dec. 22, '13 48.87 kg.	Prelim.	11:16	.....	.....	..	.....	.....	.....	.....	.....	38.65
	1	12:36	87.23	28.77	.94	37.28	0.705	98.85	97.57	112.39	39.05
	2	1:36	28.84	22.32	.94	28.28	0.529	76.65	73.08	88.65	39.47
	3	2:36	28.86	22.21	.95	29.24	0.529	76.39	74.60	78.88	39.59
Morris S. .... Dec. 23, '13 48.60 kg.	Prelim.	11:06	.....	.....	..	.....	.....	.....	.....	.....	38.04
	1	12:06	23.51	21.45	.80	25.82	0.428	71.21	68.75	73.19	38.16
	2	1:06	23.94	21.92	.80	25.39	0.428	72.73	70.84	80.86	38.46
	3	2:06	24.35	22.79	.78	25.38	0.428	75.82	69.85	76.84	38.66
Morris S. .... Jan. 2, '14 49.26 kg.	Prelim.	11:16	.....	.....	..	.....	.....	.....	.....	.....	36.97
	1	12:16	19.10	16.62	.84	19.75	0.386	55.63	58.53	52.15	36.85
	2	1:16	19.27	17.07	.82	20.20	0.386	56.94	57.89	64.93	37.05
	3	2:16	19.80	18.38	.78	22.05	0.386	60.77	61.54	60.88	37.07



—IN TYPHOID FEVER—(Continued)

Surface Temp., C.	Average Pulse	Work Added., Cm.	Non-Protein, R. Q.	Per Cent. Calories from			Calories Per Hour		Remarks
				Protein	Fat	Carbo-hyd.	Per Kg	Per Sq. M.	
38.37									
38.66	112	18.5	.85	20	42	38	1.72	50.83	9:25:10:15, protein meal: 8.7 gm. N. Began to sweat at end of second hour.
38.12	122	12.2	.83	18	49	33	1.89	55.80	
37.76	119	9.5	.78	18	62	20	1.90	55.89	
38.87									
38.59	112	5.5	.77	11	70	19	1.79	51.83	Basal. Patient restless in second period.
38.18	119	11.0+	.75	11	75	14	1.77	51.81	
37.53	123	12.0	.75	11	77	12	1.78	51.67	
35.60									
35.52	91	3.8	.85	11	46	43	1.40	41.59	9:03-9:30, protein meal: 10.6 gm. N.
35.69	94	18.6	.83	10	51	39	1.45	42.95	
35.73	98	14.5	.85	10	45	45	1.49	44.12	
35.82									
35.64	74	9.0	.82	15	52	33	1.17	34.64	Basal. Asleep in first period.
35.82	88	9.2	.85	15	43	42	1.21	35.73	
35.98	87	7.5	.80	14	59	27	1.31	38.62	
35.98									
35.54	83	6.0	1.01	16	..	84	1.32	38.95	At 10:13, 115 gm. commercial glucose.
35.72	102	5.1	1.07	15	..	85	1.38	40.77	
35.75	100	1.2	1.09	15	..	85	1.37	40.50	
35.99									
35.93	84	5.7	.94	13	18	69	1.28	37.65	Basal.
35.95	87	2.5	.88	13	35	52	1.30	38.27	
36.00	93	7.0	.85	12	46	42	1.36	40.10	
37.52									
37.29	105	0.3	.93	17	20	63	1.54	45.64	At 10:26, 115 gm. commercial glucose.
37.64	121	7.3	1.00	17	1	82	1.61	47.81	
37.71	121	2.0	.94	16	19	65	1.65	48.92	
37.49									
37.59	106	1.6	.76	20	67	13	1.55	45.13	Basal.
37.87	114	8.1	.79	19	77	4	1.63	47.86	
37.91	117	2.2	.77	18	64	18	1.65	48.00	
36.85									
37.44	109	9.2	.98	19	6	75	1.52	45.07	At 10:24, 115 gm. commercial glucose. First period 1 hr. 20 min. because patient moved at end of hour.
37.67	120	6.5	.97	18	8	74	1.57	46.61	
37.71	120	1.2	.98	18	6	76	1.57	46.44	
36.64									
36.62	99	1.2	.80	19	58	23	1.46	43.42	Basal.
36.80	100	9.2	.79	16	59	25	1.50	44.35	
37.07	105	4.0	.77	15	66	19	1.55	45.93	
35.49									
35.57	69	8.8	.84	18	44	38	1.13	33.63	Basal.
35.57	76	1.6	.83	18	42	39	1.15	34.43	
35.71	79	4.6	.78	17	57	26	1.23	39.74	

TABLE 5.—CLINICAL CALORIMETRY

Subject Date Weight	Period	End of Period	Carbon- dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.	Direct Calo- rimetry (Rectal Temp.) Cal.	Rectal Temp. C.
Morris S. .... Jan. 27, '14 57.50 kg.	Prelim.	11:45	.....	.....	..	.....	.....	.....	.....	.....	37.06
	1	12:45	19.39	17.28	.82	21.44	0.365	57.63	69.67	56.44	36.79
	2	1:45	22.28	19.73	.82	21.96	0.365	65.98	71.20	73.22	36.90
	3	2:45	22.21	19.73	.82	22.74	0.365	65.94	70.02	72.00	36.97
Morris S. .... Dec. 17, '14 61.21 kg.	Prelim.	11:27	.....	.....	..	.....	.....	.....	.....	.....	36.89
	1	12:27	21.46	19.30	.81	25.58	0.381	64.27	70.65	64.61	36.70
	2	1:27	23.25	21.17	.80	27.85	0.381	70.42	72.99	70.69	36.79
	3	2:27	23.02	20.52	.82	27.74	0.381	68.53	72.30	68.84	36.81
Morris S. .... Dec. 18, '14 62.81 kg.	Prelim.	11:00	.....	.....	..	.....	.....	.....	.....	.....	37.02
	1	12:00	27.56	22.40	.90	31.97	0.409	76.21	77.07	71.53	36.92
	2	1:00	29.29	24.39	.87	34.09	1.101	81.43	84.04	82.67	36.94
	3	2:00	23.14	19.14	.88	29.33	1.101	63.50	76.85	73.79	36.89
	4	3:00	25.29	21.01	.88	31.79	1.101	69.82	78.61	74.47	36.85
Charles F. .... Nov. 10, '13 57.73 kg.	Prelim.	11:10	.....	.....	..	.....	.....	.....	.....	.....	38.94
	1	12:10	26.83	24.23	.81	26.28	0.514	80.56	66.11	79.70	39.21
	2	1:10	27.37	25.08	.79	28.78	0.514	83.17	71.87	73.83	39.26
	3	2:10	27.91	25.99	.78	43.30	0.514	85.05	88.09	77.90	39.05
Charles F. .... Nov. 11, '13 58.22 kg.	Prelim.	11:20	.....	.....	..	.....	.....	.....	.....	.....	38.82
	1	12:20	28.97	24.58	.86	25.84	0.930	82.03	67.32	78.05	39.05
	2	1:20	30.21	26.74	.82	31.12	0.930	88.58	77.70	86.06	39.25
	3	2:20	31.40	27.66	.83	31.13	0.930	91.78	82.04	99.99	39.63
Charles F. .... Nov. 14, '13 57.94 kg.	Prelim.	11:10	.....	.....	..	.....	.....	.....	.....	.....	39.62
	1	12:10	32.69	26.60	.89	32.29	0.813	89.98	83.73	83.31	39.62
	2	1:10	31.92	25.64	.91	32.26	0.813	87.23	81.28	68.87	39.37
	3	2:10	32.24	26.33	.89	32.95	0.813	88.98	89.47	91.35	39.49
Charles F. .... Nov. 15, '13 57.03 kg.	Prelim.	11:16	.....	.....	..	.....	.....	.....	.....	.....	39.77
	1	12:16	28.26	26.44	.78	28.84	0.657	87.09	75.09	82.25	39.93
	2	1:16	28.23	26.08	.79	32.35	0.657	86.12	86.12	74.34	39.88
Charles F. .... Nov. 29, '13 50.96 kg.	Prelim.	11:26	.....	.....	..	.....	.....	.....	.....	.....	36.71
	1	12:26	21.39	18.31	.85	29.25	0.483	61.69	61.79	59.74	36.67
	2	1:26	22.05	20.15	.80	28.24	0.483	67.01	63.78	75.00	37.00
	3	2:26	21.99	19.44	.82	27.10	0.483	65.08	63.75	72.92	37.25
Charles F. .... Dec. 8, '13 50.99 kg.	Prelim.	11:10	.....	.....	..	.....	.....	.....	.....	.....	36.90
	1	12:10	25.97	19.63	.96	21.83	0.817	66.98	62.72	52.64	36.67
	2	1:10	26.73	21.61	.90	25.30	0.817	72.92	70.29	75.47	36.85
	3	2:10	25.97	21.12	.90	29.04	0.817	71.13	74.23	76.85	36.95
Charles F. .... Dec. 9, '13 50.38 kg.	Prelim.	11:06	.....	.....	..	.....	.....	.....	.....	.....	36.78
	1	12:06	22.60	18.05	.91	19.36	0.380	61.66	58.80	55.10	36.70
	2	1:06	22.10	17.29	.93	22.22	0.380	59.30	64.40	69.90	36.87
	3	2:06	21.98	17.63	.91	22.36	0.380	60.15	61.83	61.55	36.88
Charles F. .... Dec. 10, '13 51.09 kg.	Prelim.	11:10	.....	.....	..	.....	.....	.....	.....	.....	36.89
	1	12:10	26.08	20.24	.97	22.40	0.362	70.28	62.46	58.29	36.60
	2	1:10	27.70	19.45	1.04	24.37	0.362	68.24	68.32	64.48	36.76
	3	2:10	25.68	18.90	.99	28.76	0.362	65.28	72.63	60.44	36.55

—IN TYPHOID FEVER—(Continued)

Surface Temp., C.	Average Pulse	Work Added., Cm.	Non-Protein, R. Q.	Per Cent. Calories from			Calories Per Hour		Remarks
				Protein	Fat	Carbo-hyd.	Per Kg.	Per Sq. M.	
35.61									
35.11	60	0.5	.82	17	51	32	1.00	31.29	Basal.
35.15	71	5.6	.82	15	51	34	1.15	35.82	
35.37	68	5.2	.82	15	52	33	1.15	35.80	
.....	62	4.0	.81	16	55	29	1.05	33.61	Basal.
.....	65	6.0	.80	14	58	28	1.15	36.83	
.....	62	5.0	.82	15	52	33	1.12	35.03	
.....	..	5.0	.91	14	21	65	1.22	39.23	At 8:40-9:40 a. m., protein meal; 9.6 gm. N.
.....	74	6.0	.92	36	17	47	1.30	41.87	
.....	70	6.0	.95	46	9	45	1.01	32.65	
.....	62	6.0	.93	42	14	44	1.11	35.90	
.....	76	3.5	.81	17	55	28	1.40	43.81	Basal.
.....	76	2.0	.79	16	60	24	1.44	45.23	
.....	82	9.0	.78	16	64	20	1.49	46.74	
37.09									
38.24	77	3.5	.88	30	28	42	1.41	44.34	9:10-10:10, protein meal; Nitrogen 6.6 gm.
38.25	80	13.0	.83	28	42	30	1.52	47.88	
38.34	84	4.0	.83	27	41	32	1.57	49.61	
38.79									
38.90	97	15.0	.93	31	19	50	1.56	48.80	At 10:21 a. m., 115 gm commercial glucose.
38.68	98	8.3	.94	25	15	60	1.52	47.31	
38.79	96	25.0	.92	24	21	55	1.55	48.25	
38.92									
39.10	90	17.0	.77	20	43	37	1.53	47.75	Basal.
39.04	88	15.5	.78	20	39	41	1.51	47.22	
.....	80	13.2	.86	21	37	42	1.23	36.81	Basal.
.....	80	16.5	.79	20	36	44	1.33	39.68	
.....	84	18.8	.82	20	47	33	1.30	38.83	
39.24									
39.54	74	38.6	1.05	32	..	68	1.31	39.54	9:03-9:45, protein meal; 10.5 gm. N. Work added too high on account of rapid changes in barometer.
39.16	72	20.3	.94	30	18	52	1.43	43.05	
39.37	84	15.0	.94	30	17	53	1.40	41.99	
.....									
.....	75	22.3	.92	16	40	45	1.23	36.72	Basal.
.....	76	23.0	.96	17	42	41	1.18	35.32	
.....	84	20.7	.92	17	30	53	1.20	35.83	
.....									
.....	78	10.0	1.00	14	..	86	1.38	41.46	At 10:27, 115 gm. commercial glucose.
.....	87	23.5+27	1.08	14	..	86	1.34	40.26	
.....	81	28.0+27	1.02	15	..	85	1.29	38.81	

TABLE 5.—CLINICAL CALORIMETRY—

Subject Date Weight	Period	End of Period	Carbon- dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.	Direct Calo- rimetry (Rectal Temp.) Cal.	Rectal Temp. C.	
Charles F. .... Dec. 26, '13 55.87 kg.	Prelim.	11:12	.....	.....	..	.....	.....	.....	.....	.....	36.84	
	1	12:12	23.75	19.16	.90	26.72	0.275	65.56	75.47	75.27	36.90	
	2	1:12	21.98	18.86	.85	25.23	0.275	63.65	69.83	67.08	36.86	
	3	2:12	22.11	20.10	.80	25.14	0.275	67.03	70.63	69.23	36.85	
Charles F. .... Dec. 31, '13 55.98 kg.	Prelim.	1:40	.....	.....	..	.....	.....	.....	.....	.....	37.08	
	1	2:40	21.85	19.82	.80	22.56	0.403	65.85	66.09	59.70	36.95	
	2	3:40	22.81	21.14	.78	26.98	0.403	69.98	69.09	68.75	36.95	
Howard F. .... Nov. 7, '13 35.47 kg.	Prelim.	11:16	.....	.....	..	.....	.....	.....	.....	.....	39.74	
	1	12:16	22.09	20.53	.78	22.79	.....	68.25	57.28	56.71	39.73	
	2	1:16	21.02	19.75	.77	24.24	.....	65.53	64.17	63.90	39.73	
	3	2:16	20.86	.....	..	24.06	.....	65.03 ?	64.99	60.30	39.58	
Howard F. .... Nov. 12, '13 34.98 kg.	Prelim.	11:24	.....	.....	..	.....	.....	.....	.....	.....	39.64	
	1	12:24	22.06	19.37	.83	20.58	0.612	64.40	58.89	61.38	39.74	
	2	1:24	23.23	20.40	.83	23.38	0.612	67.88	63.72	65.61	39.89	
	3	2:24	22.55	21.27	.77	23.60	0.612	69.78	63.49	70.09	40.15	
Howard F. .... Nov. 13, '13 34.19 kg.	Prelim.	11:00	.....	.....	..	.....	.....	.....	.....	.....	39.76	
	1	12:00	19.45	17.76	.80	22.30	0.436	58.81	57.80	59.64	39.84	
	2	1:00	19.64	18.48	.77	22.62	0.436	60.86	58.19	57.19	39.82	
	3	2:00	20.20	19.24	.76	23.66	0.436	63.22	63.74	62.17	39.76	
Howard F. .... Nov. 20, '13 32.54 kg.	Prelim.	11:30	.....	.....	..	.....	.....	.....	.....	.....	39.31	
	1	12:30	18.43	17.26	.78	27.43	0.354	56.98	55.72	56.87	39.33	
	2	1:30	18.27	17.42	.76	27.31	0.354	57.30	63.70	58.16	39.14	
	3	2:30	17.96	17.42	.75	25.62	0.354	57.10	59.75	63.97	38.94	
Howard F. .... Dec. 1, '13 32.93 kg.	Prelim.	11:06	.....	.....	..	.....	.....	.....	.....	.....	37.03	
	1	12:06	19.35	14.58	.97	18.80	0.292	50.50	45.34	42.26	36.93	
	2	1:06	39.56	29.26	.98	37.03	0.292	101.68	{ 46.88 }		97.14	{ 36.96 }
	3	2:06							{ 50.17 }			
Howard F. .... Dec. 2, '13 33.06 kg.	Prelim.	11:12	.....	.....	..	.....	.....	.....	.....	.....	38.84	
	1	12:12	15.46	12.42	.91	17.57	0.234	42.40	44.03	42.30	36.79	
	2	1:12	18.09	13.48	.98	18.64	0.234	46.86	50.53	52.20	36.93	
Howard F. .... Dec. 5, '13 34.74 kg.	Prelim.	11:06	.....	.....	..	.....	.....	.....	.....	.....	37.07	
	1	12:06	22.13	17.28	.93	21.01	0.614	58.85	55.03	51.80	36.97	
	2	1:06	21.24	17.61	1.00	21.99	0.614	60.75	61.84	64.82	37.17	
	3	2:06	24.72	19.43	.93	23.61	0.614	66.21	64.12	65.52	37.25	
Howard F. .... Dec. 6, '13 33.78 kg.	Prelim.	10:56	.....	.....	..	.....	.....	.....	.....	.....	37.02	
	1	11:56	18.20	13.44	.98	17.44	0.267	46.71	47.88	46.67	36.99	
	2	12:56	19.17	14.84	.94	18.30	0.267	51.14	51.37	51.43	37.06	
Howard F. .... Dec. 18, '13 37.17 kg.	Prelim.	11:06	.....	.....	..	.....	.....	.....	.....	.....	37.11	
	1	12:06	19.11	16.10	.86	18.73	0.314	54.38	53.61	52.94	37.10	
	2	1:06	21.42	18.19	.86	20.04	0.314	61.42	58.80	63.36	37.29	
	3	2:06	20.93	18.62	.81	23.84	0.314	62.26	65.14	63.04	37.25	

## IN TYPHOID FEVER—(Continued)

Surface Temp., C.	Average Pulse	Work Added, Cm.	Non-Protein, R. Q.	Per Cent. Calories from			Calories Per Hour		Remarks
				Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M.	
36.02									
36.09	76	23.2	.92	11	26	63	1.18	36.44	Basal
36.38	..	18.3	.85	11	44	45	1.14	35.38	
35.74	..	10.2	.80	11	61	28	1.20	37.26	
36.90									
35.98	78	4.0	.80	16	57	27	1.18	36.38	Basal.
36.68	81	....	.78	15	64	21	1.25	38.66	
.....	100	10.0	....	..	..	..	1.91	51.35	Basal. Urine not obtained; O <sub>2</sub> lost in third period.
.....	103	6.0	....	..	..	..	1.83	49.31	
.....	106	2.0	....	..	..	..	1.83(?)	48.93(?)	
39.01									
39.13	105	2.5	.84	25	41	34	1.84	48.90	9:10-9:40, protein meal; 6.5 gm. N. Asleep most of first period.
39.30	104	9.5	.84	24	42	34	1.94	51.55	
39.76	105	5.5	.76	23	63	14	2.00	52.99	
.....	108	1.0	.79	20	56	24	1.72	45.34	Basal.
.....	108	2.5	.77	19	65	16	1.78	46.92	
.....	104	7.7	.75	18	79	13	1.85	48.74	
39.14									
38.89	103	9.6	.77	16	65	19	1.75	45.41	Basal.
38.68	102	9.6	.75	16	70	14	1.76	45.66	
38.88	92	9.5	.74	16	75	9	1.75	45.50	
37.19									
37.16	98	2.6	1.00	15	1	84	1.53	39.92	At 10:19, 115 gm. commercial glucose; second and third periods averaged.
36.63	97	5.1	1.02	15	..	85	1.50	40.19	
37.31	97	6.0							
39.32									
36.83	75	2.5	.92	15	22	63	1.28	33.39	Basal. Asleep most of first hour.
36.60	76	15.6	1.01	13	..	87	1.42	36.90	
.....	91	7.0	.99	28	3	69	1.70	44.90	9:00-10:00, protein meal; 10.2 gm. N. Asleep first period.
.....	96	20.5	1.08	27	..	73	1.75	46.34	
.....	93	6.5(?)	.97	25	8	67	1.91	50.51	
.....	73	6.6	1.02	15	..	85	1.33	38.31	Basal. Asleep one-half first period.
.....	76	14.2	.96	14	11	75	1.51	39.75	
36.61									
36.92	104	5.5	.87	15	27	43	1.46	39.66	Basal. Asleep first period.
37.00	112	13.0	.87	14	40	46	1.65	44.79	
36.76	105	17.3	.82	12	33	54	1.68	45.40	

TABLE 5.—CLINICAL CALORIMETRY—

Subject Date Weight	Period	End of Period	Carbon- dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.	Direct Calo- rimetry (Rectal Temp.) Cal.	Rectal Temp. C.
Howard F. .... Dec. 30, '13 39.40 kg.	Prelim.	1:30	.....	.....	..	.....	.....	.....	.....	.....	37.1
	1	2:30	19.66	17.18	.83	22.45	0.278	57.68	62.50	55.92	37.1
	2	3:30	20.74	18.62	.81	23.93	0.278	62.21	60.31	61.45	37.1
Karl S. .... Jan. 5, '14 54.64 kg.	Prelim.	11:50	.....	.....	..	.....	.....	.....	.....	.....	40.1
	1	12:50	30.78	29.50	.76	39.97	0.720	96.73	101.70	91.12	39.9
	2	1:50	29.73	28.53	.76	42.23	0.720	93.48	104.45	93.03	39.7
Karl S. .... Jan. 6, '14 54.52 kg.	Prelim.	12:30	.....	.....	..	.....	.....	.....	.....	.....	39.5
	1	1:30	34.01	29.51	.84	26.77	0.879	98.46	87.72	112.04	40.0
	2	2:30	35.13	31.49	.81	34.31	0.879	104.43	104.39	99.22	40.0
	3	3:30	35.32	31.56	.81	38.70	0.879	104.75	107.68	105.06	40.0
Karl S. .... Jan. 16, '14 52.21 kg.	Prelim.	10:50	.....	.....	..	.....	.....	.....	.....	.....	38.2
	1	11:50	26.55	25.94	.74	26.51	0.786	84.44	.....	.....	38.3
	2	1:02	32.49	28.88	.82	38.71	0.943	95.01	.....	.....	38.2
	3	1:50	21.52	19.72	.80	32.34	0.655	64.72	.....	.....	38.1
Karl S. .... Jan. 19, '14 51.19 kg.	Prelim.	10:50	.....	.....	..	.....	.....	.....	.....	.....	36.8
	1	11:50	20.70	16.34	.92	12.72	0.522	55.62	.....	.....	36.8
	2	12:50	22.68	18.41	.87	28.28	0.522	62.03	.....	.....	36.8
	3	1:50	22.53	19.41	.84	32.55	0.522	64.98	.....	.....	36.8
Karl S. .... Jan. 21, '14 51.29 kg.	Prelim.	12:30	.....	.....	..	.....	.....	.....	.....	.....	36.1
	1	1:30	24.09	19.71	.89	32.46	0.858	66.11	.....	.....	36.1
	2	2:30	23.96	19.57	.89	25.79	0.858	65.65	.....	.....	36.1
	3	3:30	26.95	21.45	.91	32.17	0.858	72.55	.....	.....	36.1
Karl S. .... Jan. 22, '14 50.63 kg.	Prelim.	12:40	.....	.....	..	.....	.....	.....	.....	.....	36.1
	1	1:40	18.66	15.37	.88	16.87	0.428	51.92	.....	.....	36.1
	2	2:40	21.01	16.98	.90	20.51	0.428	57.70	.....	.....	36.1
	3	3:40	20.54	17.06	.88	22.17	0.428	57.62	.....	.....	36.1
Karl S. .... Feb. 6, '14 53.30 kg.	Prelim.	11:05	.....	.....	..	.....	.....	.....	.....	.....	37.1
	1	12:05	23.16	20.28	.83	23.98	0.324	68.07	67.32	58.11	36.1
	2	1:05	21.97	18.82	.85	22.85	0.324	63.43	67.46	56.97	36.1
	3	2:05	25.49	24.36	.76	27.16	0.324	80.44	74.45	80.28	36.1
Karl S. .... Feb. 7, '14 54.45 kg.	Prelim.	10:46	.....	.....	..	.....	.....	.....	.....	.....	37.1
	1	11:46	27.92	22.71	.89	32.41	0.581	77.05	77.13	60.51	36.1
	2	12:46	27.33	21.87	.91	29.12	0.581	74.43	79.33	74.46	36.1
	3	1:46	26.23	21.16	.90	32.41	0.581	71.85	79.75	76.71	36.1
Thomas B. .... Oct. 15, '13 73.62 kg.	Prelim.	10:48	.....	.....	..	.....	.....	.....	.....	.....	36.1
	1	11:48	24.87	22.60	.80	23.50	0.505	75.00	48.97	70.72	37.1
	2	12:48	27.05	22.82	.86	24.88	0.505	76.95	56.97	72.61	37.1
	3	1:48	26.46	24.69	.78	26.46	0.505	81.57	63.67	74.67	37.1
	4	2:48	28.39	24.58	.84	28.78	0.505	82.49	67.68	79.68	37.1
Thomas B. .... Oct. 21, '13 72.56 kg.	Prelim.	10:24	.....	.....	..	.....	.....	.....	.....	.....	36.1
	1	11:24	22.98	20.14	.88	24.71	0.407	67.43	.....	52.61	36.1
	2	12:24	24.90	19.11	.95	29.65	0.407	65.88	65.03	63.75	36.1
	3	1:24	26.13	20.21	.94	30.15	0.407	69.58	68.06	62.32	36.1



# N TYPHOID FEVER—(Continued)

Surface temp., C.	Average Pulse	Work Adder., Cm.	Non- Protein, R. Q.	Per Cent. Calories from			Calories Per Hour		Remarks
				Pro- tein	Fat	Carbo- hyd.	Per Kg.	Per Sq. M.	
36.37									
36.44	100	6.5	.84	13	48	39	1.47	40.49	Basal. Asleep greater part of both periods.
36.60	107	8.5	.81	12	57	31	1.58	43.67	
36.24									
38.97	114	8.4	.75	20	60	11	1.77	54.93	Basal.
38.67	109	6.7	.75	20	60	11	1.71	53.08	
38.00									
38.61	107	8.8	.85	24	39	37	1.80	55.62	9:45-10:12, protein meal; 10.5 gm. N.
38.35	99(?)	14.6	.81	22	50	28	1.92	59.00	
38.27	119	13.0	.82	22	49	29	1.92	59.18	
	92	12.2	.72	25	70	5	1.62	49.09	Basal. Water ther. broken. Second period 72 min. long on ac- count movement.
	96	21.0+3?	.82	26	44	30	1.53	46.03	
	96	11.0	.77	26	57	17	1.55	45.15	
	76	10.6	.86	25	9	66	1.09	32.74	Basal.
	76	14.8+4	.89	22	28	50	1.21	36.51	
	78	16.8	.86	21	30	40	1.27	38.25	
	73	9.8	.94	34	14	62	1.29	38.89	9:35-11:36, protein meal; 10.0 gm. N.
	69	5.7	.94	35	13	62	1.28	38.62	
	74	17.0	.97	31	7	62	1.42	42.68	
	59	4.0	.91	22	25	53	1.03	30.81	Basal. Asleep first period.
	57	11.7	.93	20	20	60	1.14	34.24	
	68	9.2	.90	20	29	51	1.14	34.20	
36.20									
36.52	81	10.5	.84	13	49	38	1.28	39.02	Basal. Asleep about 30 min. in first period and 60 min. in second.
36.86	79	8.4	.86	14	42	44	1.19	36.37	
36.97	82	10.2	.76	11	74	15	1.51	46.12	
36.40									
36.58	94	12.4	.92	29	22	58	1.41	43.66	7:20-7:40, 44.3 gm. pro- tein; 9:35-9:37, 15.6 gm. protein; total, 9.6 gm. N. Asleep most of the time.
36.97	90	7.0	.94	21	16	63	1.37	42.07	
36.34	86	11.0	.93	21	19	60	1.32	40.62	
	81	8.0	.80	18	56	26	1.02	34.67	Basal.
	85	14.0	.88	17	35	48	1.05	35.58	
	84	7.6	.77	16	65	19	1.11	37.71	
	91	11.0	.85	19	43	41	1.12	38.14	
	78(?)	12.0	.84	16	47	37	0.93	31.48	Basal.
	78	10.0	.98	16	6	78	0.91	30.76	
	84	.....	.97	16	9	75	0.96	32.48	

TABLE 5.—CLINICAL CALORIMETRY.—

Subject Date Weight	Period	End of Period	Carbon- dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.	Direct Calo- rimetry (Rectal Temp.) Cal.	Rectal Temp. C.
Richard T. .... Oct. 18, '13 36.49 kg.	Prelim.	9:48	.....	.....	..	.....	.....	.....	.....	.....	38.0
	1	10:48	20.39	18.59	.50	30.29	0.403	61.65	43.77	57.62	38.60
	2	11:48	21.05	18.24	.84	21.24	0.403	61.12	42.57	66.86	39.50
	3	12:48	20.49	18.68	.80	25.61	0.403	61.95 ?	45.94	62.35	39.74
Richard T. .... Oct. 26, '13 35.37 kg.	Prelim.	10:16	.....	.....	..	.....	.....	.....	.....	.....	37.68
	1	11:16	18.98	15.18	.91	31.21	0.499	51.48	42.37	58.44	38.24
	2	12:16	21.25	18.39	.84	31.41	0.499	61.49	47.46	58.51	38.63
	3	1:16	19.90	17.96	.81	29.74	0.499	59.49	48.42	46.90	38.63
Anton K. .... Oct. 16, '13 50.55 kg.	Prelim.	11:16	.....	.....	..	.....	.....	.....	.....	.....	36.9
	1	12:16	22.48	18.64	.88	30.88	0.470	62.98	61.00	61.00	36.9
	2	1:16	21.65	19.08	.83	33.40	0.470	63.64	66.45	72.34	37.1
	3	2:16	23.57	19.73	.87	30.29	0.479	66.57	64.84	68.64	37.2
Rose G. .... Nov. 22, '13 30.11 kg.	Prelim.	11:04	.....	.....	..	.....	.....	.....	.....	.....	37.0
	1	12:04	17.77	15.73	.82	28.24	.....	52.81	51.24	53.76	37.1
	2	12:34	9.28	7.28	.93	17.44	.....	24.98	28.36	24.99	37.0
Edw. B. .... Oct. 23, '14 55.76 kg.	Prelim.	12:07	.....	.....	..	.....	.....	.....	.....	.....	38.0
	1	1:07	25.02	22.61	.81	30.22	0.187	75.66	62.23	70.20	38.2
	2	2:07	25.51	23.48	.79	28.78	0.187	78.30	64.70	81.43	38.8
	3	3:07	27.24	25.59	.77	29.84	0.187	85.03	70.05	71.67	38.8
Edw. B. .... Oct. 26, '14 56.10 kg.	Prelim.	11:24	.....	.....	..	.....	.....	.....	.....	.....	37.5
	1	12:24	23.13	19.58	.86	31.21	0.264	66.36	61.58	66.23	37.6
	2	1:24	24.87	23.79	.76	29.49	0.264	78.72	60.08	67.98	37.8
	3	2:24	25.18	22.90	.80	30.36	0.264	76.47	65.45	73.34	38.0
	4	3:24	26.12	23.21	.82	31.13	0.264	77.87	70.55	84.46	38.1
Edw. B. .... Oct. 27, '14 56.84 kg.	Prelim.	11:20	.....	.....	..	.....	.....	.....	.....	.....	37.6
	1	12:20	24.80	21.91	.82	30.89	0.552	73.08	60.09	59.69	37.6
	2	1:20	23.76	22.13	.78	29.26	0.552	73.01	61.33	70.63	37.6
	3	2:20	23.24	22.30	.76	28.83	0.552	73.13	63.78	73.06	37.6
Edw. B. .... Nov. 4, '14 58.72 kg.	Prelim.	11:15	.....	.....	..	.....	.....	.....	.....	.....	37.7
	1	12:15	24.00	19.79	.88	31.79	0.337	67.32	64.06	64.69	37.7
	2	1:15	25.03	21.77	.84	31.06	0.337	73.17	65.16	69.21	37.7
	3	2:15	24.89	21.98	.82	31.62	0.337	73.72	70.13	74.19	37.7
Edw. B. .... Nov. 6, '14 59.78 kg.	Prelim.	11:15	.....	.....	..	.....	.....	.....	.....	.....	38.0
	1	12:15	26.21	23.22	.82	27.40	0.336	77.76	69.39	81.16	39.0
	2	1:15	26.65	23.45	.83	28.17	0.336	78.07	64.20	69.44	39.0
	3	2:15	26.61	23.39	.82	30.30	0.336	78.33	68.49	72.75	39.0
Edw. B. .... Nov. 10, '14 56.87 kg.	Prelim.	11:15	.....	.....	..	.....	.....	.....	.....	.....	40.0
	1	12:15	30.59	30.14	.74	35.32	0.525	98.74	88.56	80.50	40.0
	2	1:15	29.52	27.49	.78	36.30	0.525	90.99	87.53	91.26	40.0
	3	2:15	30.25	.....	..	39.54	0.525	.....	94.67	86.34	40.0
John K. .... Dec. 15, '14 63.81 kg.	Prelim	11:56	.....	.....	..	.....	.....	.....	.....	.....	39.0
	1	12:56	30.97	28.17	.80	34.02	1.258	92.29	85.30	94.23	39.0
	2	1:56	30.50	30.08	.74	39.95	1.258	97.14	91.58	87.82	39.0

N TYPHOID FEVER—(Continued)

Surface Temp., C.	Average Pulse	Work Added., Cm.	Non-Protein, R. Q.	Per Cent. Calories from			Calories Per Hour		Remarks
				Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M.	
.....	81	31.4	.80	17	57	26	1.69	45.50	Basal. Somewhat restless.
.....	98	16.2	.85	17	43	40	1.68	45.11	
.....	..	18.5	.80	17	57	26	1.70	45.72	
.....	82	22.0	.95	26	13	61	1.45	38.79	Basal.
.....	102	30.0	.85	22	40	38	1.74	46.34	
.....	95	17.0	.81	22	50	28	1.68	44.83	
.....	76	21.0	.90	20	28	52	1.25	37.42	Basal.
.....	81	19.0	.83	20	46	34	1.26	37.81	
.....	80	13.0	.89	19	32	49	1.32	39.55	
35.75									
36.05	79	16.0	....	..	..	..	1.75	44.32	Basal. Restless. Second period ½ hr. long because patient voided in bed.
36.10	76	9.0	....	..	..	..	1.66	41.93	
.....	118	12.0	.81	7	49	44	1.36	42.10	Basal.
.....	115	17.0	.79	6	67	27	1.40	43.57	
.....	116	24.0	.77	6	73	21	1.53	47.32	
.....	105	11.0	.87	11	39	50	1.18	36.78	10:25 a. m., 79 gm. olive oil = 750 calories.
.....	117	10.0	.76	9	74	17	1.40	43.64	
.....	126	10.0	.80	9	62	29	1.36	42.39	
.....	123	15.0	.82	9	56	35	1.39	43.17	
.....	106	14.0	.83	19	47	34	1.29	40.16	Basal.
.....	109	22.0	.78	19	61	20	1.29	40.12	
.....	107	14.0	.75	19	69	12	1.29	40.18	
.....	102	10.6	.90	13	30	57	1.15	36.19	Basal.
.....	104	14.0	.84	12	48	40	1.25	39.34	
.....	105	25.0	.83	12	51	37	1.26	39.64	
.....	...	31.0	.82	11	54	35	1.30	41.82	Basal. Rising temp.
.....	124	5.0	.83	11	51	38	1.31	41.48	
.....	124	12.0	.82	11	54	35	1.31	41.62	
.....	141	24.0	.73	14	79	7	1.74	54.31	Basal. Very high temp. Mildly delirious.
.....	142	20.5	.78	15	64	21	1.60	50.05	
.....	140	16.0++							
.....	62	16.0	.80	26	43	21	1.45	46.94	Basal.
.....	63	14.0	.70	34	66	6	1.52	49.41	

TABLE 6.—CLINICAL DATA  
CHARLES F.

Date, 1913	Food			Food N., Gm.	Urine N., Gm.	Excreta N., Gm.	Nitrogen Bal., Gm.	Body Wt., Kg.	Urine Vol., C.c.
	Total Calories	Carbohy- drate, Gm.	Fat, Gm.						
Nov. 6....	1,465	88.0	96.0	8.3	14.68	15.51†	-7.21	58.56	1,270
Nov. 7....	.....	.....	.....	....	15.52	.....	.....	.....	1,600
Nov. 8....	1,855	116.0	123.0	9.1	21.10	22.01	-12.91	.....	2,300
Nov. 9....	2,065	130.0	135.0	10.8	20.45	21.53	-10.73	.....	1,870
Nov. 10....	1,088	80.0	69.0	4.4	16.22	16.66	-12.26	57.76	1,205
Nov. 11....	2,027	214.0	87.0	13.2	22.23	23.60	-10.40	58.25	1,740
Nov. 12....	2,610	251.0	144.0	9.8	18.92	19.90	-10.10	.....	2,110
Nov. 13....	2,255	218.0	118.0	10.2	17.37	18.39	-8.19	57.83	1,900
Nov. 14....	1,399	203.0	50.0	3.9	16.03	16.41	-12.61	57.60	1,235
Nov. 15....	1,286	148.0	60.0	4.6	18.54	19.00	-14.40	56.86	1,270
Nov. 16....	1,440	151.0	72.0	5.7	18.89	19.46	-13.76	.....	1,960
Nov. 17....	1,492	128.0	83.0	7.6	17.82	18.58	-10.98	.....	2,110
Nov. 18....	1,749	133.0	107.0	8.1	20.34	21.15	-13.05	56.01	1,470
Nov. 19....	1,019	63.0	68.0	5.2	22.13	22.65	-17.45	.....	1,360
Nov. 20....	1,323	93.0	76.0	8.7	22.41	23.28	-14.53	.....	1,380
Nov. 21....	1,426	74.0	98.0	8.1	22.81	23.62	-15.52	.....	1,330
Nov. 22....	1,970	122.0	128.0	10.9	20.50	21.59	-10.69	.....	1,900
Nov. 23....	1,787	112.0	115.0	10.6	18.16	19.22	-8.62	.....	1,680
Nov. 24....	1,696	117.0	101.0	10.4	18.16	19.20	-8.80	52.02	1,530
Nov. 25....	2,443	159.0	155.0	13.8	18.95	20.33	-6.53	.....	1,910
Nov. 26....	2,595	174.0	160.0	15.4	18.92	20.43	-5.06	51.48	20.50
Nov. 27....	2,345	173.0	142.0	12.3	18.41	19.64	-7.34	.....	1,920
Nov. 28....	2,646	223.0	150.0	13.1	16.65	17.96	-4.86	50.98	2,120
Nov. 29....	* 1,903	129.0	126.0	7.3	13.91	14.69	-6.89	50.29	1,150
Nov. 30....	2,825	236.0	158.0	15.2	15.58	17.10	-1.90	.....	1,700
Dec. 1....	3,491	314.0	195.0	14.9	14.12	15.61	-0.71	50.50	1,760
Dec. 2....	3,126	310.0	160.0	14.3	12.33	13.76	+0.54	.....	1,430+
Dec. 3....	2,595	279.0	118.0	13.7	11.99	13.36	+0.34	50.79	1,600
Dec. 4....	3,408	332.0	150.0	17.4	12.69	14.43	+2.96	.....	1,480
Dec. 5....	2,683	362.0	87.0	15.0	12.05	13.55	+1.45	.....	1,580
Dec. 6....	2,827	390.0	88.0	15.9	12.67	14.26	+1.64	49.83	1,401
Dec. 7....	3,223	446.0	106.0	16.0	12.72	14.32	+1.68	49.83	1,740
Dec. 8....	2,182	346.0	94.0	20.0	16.27	18.27	+1.73	51.02	1,220
Dec. 9....	2,426	308.0	91.0	12.5	12.04	13.29	-0.79	50.41	695
Dec. 10....	2,905	432.0	88.0	12.3	10.01	11.24	+1.06	50.80	1,100
Dec. 11....	3,485	503.0	107.0	16.7	9.47	11.14	+5.56	.....	1,640
Dec. 12....	3,768	556.0	115.0	16.3	9.92	11.55	+4.75	.....	1,500
Dec. 13....	4,025	619.0	129.0	18.2	10.48	12.80	+5.90	53.16	1,880
Dec. 14....	3,660	549.0	105.0	16.9	10.59	12.27	+4.53	.....	1,470

\* Estimate heat production 1,725.

TABLE 6.—CLINICAL DATA—(Continued)

CHARLES F.—(Continued)

Date, 1913	Food			Food N., Gm.	Urine N., Gm.	Excretn N., Gm.	Nitrogen Bal., Gm.	Body Wt., Kg.	Urine Vol., C.c.
	Total Calories	Carbohy- drate, Gm.	Fat, Gm.						
Dec. 15....	4,032	585.0	124.0	18.8	9.93	11.81	+6.99	52.81	1,330+
Dec. 16....	3,921	573.0	118.0	18.6	11.67	13.53	+5.07	54.05	1,280
Dec. 17....	3,539	510.0	109.0	16.9	11.15	12.84	+4.06	.....	1,470
Dec. 18....	3,869	572.0	113.0	18.2	11.54	13.86	+4.84	.....	1,800
Dec. 19....	4,085	630.0	112.0	17.9	10.39	12.19	+5.72	.....	1,500
Dec. 20....	3,901	599.0	105.0	18.5	11.04	12.89	+5.61	.....	1,760
Dec. 21....	4,017	620.0	105.0	19.3	11.43	13.36	+5.94	.....	1,850
Dec. 22....	3,351	282.0	189.0	17.1	12.33	14.04	+3.06	55.43	1,700
Dec. 23....	3,722	241.0	249.0	16.4	11.46	13.10	+3.30	.....	1,180
Dec. 24....	3,739	228.0	254.0	17.5	13.14	14.89	+2.61	.....	1,440
Dec. 25....	.....	.....	.....	....	9.28	.....	.....	.....	1,300
Dec. 26....	2,122	153.0	137.0	12.4	9.40	10.64	+1.76	55.91	1,940
Dec. 27....	3,636	254.0	224.0	20.0	12.16	14.16	+5.84	.....	1,600
Dec. 28....	3,614	247.0	226.0	19.4	12.86	14.80	+4.60	.....	1,640
Dec. 29....	3,818	221.0	259.0	19.0	12.78	14.66	+4.34	.....	1,820
Dec. 30....	4,899	256.0	347.0	24.2	11.49	13.91	+10.29	.....	1,480
Dec. 31....	2,131	202.0	103.0	13.3	11.53	12.86	+0.44	56.43	1,571
1914 Jan. 1....	3,949	347.0	161.0	18.6	11.54	13.40	+5.20	.....	1,000
Jan. 2....	3,587	287.0	202.0	22.0	8.10	10.30	+11.70	.....	860

† Excreta nitrogen estimated as urine nitrogen + 10 per cent. of food nitrogen.

TABLE 6.—CLINICAL DATA—(Continued)

MORRIS S.

Date, 1913	Esti- mated Heat Produce- tion per 24 Hrs.	Food			Food N., Gm.	Urine N., Gm.	Feces N., Gm.	Excreta N., Gm.	Nitrogen Bal., Gm.	Body Weight Kg.	Urine Volume, C.c.	Feces Fat
		Total Calories	Carbo- hydrate, Gm.	Fat, Gm.								
Oct. 23	.....	2,962	419.0	76.0	20.8	15.13	3.1*	18.2	+2.6	49.69	1,250	
Oct. 24	2,376	1,259	169.0	28.0	11.8	19.56	1.7*	21.3	-9.5	51.50	2,350	
Oct. 25	2,299	2,371	364.0	86.0	21.3	13.59	3.2*	16.8	+4.5	51.22	1,710	
Oct. 26	.....	4,375	471.0	101.0	19.5	20.34	2.9	23.2	-3.7	.....	3,000	
Oct. 27	.....	3,194	321.0	152.0	18.2	21.60	2.7	24.3	-6.1	51.26	2,170	
Oct. 28	2,200	2,332	242.0	116.0	10.0	17.43	1.5	18.9	-8.9	51.18	1,390	
Oct. 29	2,228	2,876	258.0	150.0	16.4	20.38	2.5	22.9	-6.5	50.17	1,465	
Oct. 30	.....	3,031	318.0	141.0	15.5	18.72	2.31	21.03	-5.5	49.85	1,580	9.74
Oct. 31	2,225	2,784	224.0	149.0	18.0	22.28	2.31	24.59	-6.6	50.32	1,830	9.74
Nov. 1	.....	3,089	327.0	147.0	14.8	17.48	2.31	19.79	-5.0	49.82	1,600	9.74
Nov. 2	.....	3,039	324.0	142.0	15.2	16.76	2.31	19.07	-3.9	.....	1,600	9.74
Nov. 3	2,205	3,039	324.0	142.0	15.2	17.39	2.31	19.70	-4.5	48.83	1,370	9.74
Nov. 4	.....	3,039	324.0	142.0	15.2	15.86	2.31	18.17	-3.0	49.63	1,220	9.74
Nov. 5	2,104	3,024	324.0	139.0	15.4	15.57	2.31	17.88	-2.5	48.48	1,160	9.74
Nov. 6	.....	3,039	325.0	147.0	15.4	13.51	2.3	15.8	-0.4	49.03	1,310	
Nov. 7	.....	3,034	327.0	140.0	15.0	12.39	2.3	14.7	+0.3	.....	1,220	
Nov. 8	.....	3,018	319.0	142.0	15.0	11.24	2.3	13.5	+1.5	48.73	1,310	
Nov. 9	.....	3,048	321.0	144.0	15.4	11.71	2.3	14.0	+1.4	.....	1,240	
Nov. 10	.....	2,969	305.0	144.0	14.9	12.05	2.2	14.3	+0.6	.....	2,000	
Nov. 11	.....	3,004	324.0	140.0	14.8	10.23	2.2	12.4	+2.4	48.05	1,220	
Nov. 12	.....	2,968	314.0	142.0	15.2	12.78	2.3	15.1	+0.1	.....	1,380	
Nov. 13	.....	2,998	314.0	142.0	15.2	11.43	2.3	13.7	+1.5	.....	1,480	
Nov. 14	.....	3,181	331.0	142.0	15.4	10.54	2.3	12.8	+2.6	.....	1,390	
Nov. 15	.....	2,994	313.0	142.0	15.2	10.42	2.3	12.7	+2.5	.....	2,000	
Nov. 16	.....	3,134	341.0	144.0	15.3	11.44	2.3	13.7	+1.6	.....	1,820	
Nov. 17	1,875	3,076	333.0	142.0	15.2	13.32	2.3	15.6	-0.4	48.80	1,690	
Nov. 18	2,022	1,987	217.0	95.0	8.0	15.19	1.2	16.4	-8.4	49.06	1,440	
Nov. 19	.....	1,855	148.0	61.0	7.7	15.47	1.2	16.7	-9.0	.....	2,280	
Nov. 20	.....	1,727	199.0	79.0	7.0	15.13	1.1	16.2	-9.2	.....	1,300	
Nov. 21	.....	1,865	171.0	95.0	8.4	14.74	1.3	16.0	-7.6	.....	900	
Nov. 22	.....	2,292	153.0	152.0	10.1	14.85	1.5	16.4	-6.3	.....	800	
Nov. 23	.....	2,392	192.0	132.0	10.7	15.69	1.6	17.3	-6.6	.....	840	
Nov. 24	2,282	2,016	173.0	117.0	8.5	13.08	1.3	14.4	-5.9	46.98	800	
Nov. 25	2,301	2,298	167.0	123.0	15.1	13.66	2.3	16.0	-0.9	47.47	925	
Nov. 26	2,217	2,087	172.0	126.0	8.0	10.32	1.2	11.5	-3.5	45.84	780	
Nov. 27	.....	2,747	242.0	148.0	14.8	18.88	2.2	20.8	-6.0	.....	820	
Nov. 28	.....	2,741	256.0	140.0	15.0	12.44	2.3	14.7	+0.3	47.26	980	
Nov. 29	.....	3,033	324.0	142.0	15.0	11.82	2.3	14.1	+0.9	.....	1,370	
Nov. 30	.....	3,153	334.0	147.0	16.0	10.76	2.4	13.2	+2.8	.....	1,060	
Dec. 1	...	3,091	333.0	142.0	15.7	9.81	2.4	12.2	+3.5	47.08	1,180	
Dec. 2	.....	3,090	340.0	142.0	15.3	9.69	2.3	12.0	+3.3	.....	1,660+	

\* Feces analyzed October 30 to November 5. Feces nitrogen averaged 14.8 per cent. of food nitrogen. On all other days the feces nitrogen was calculated as 15 per cent. of food nitrogen.



TABLE 6.—CLINICAL DATA—(Continued)

MORRIS S.—(Continued)

Date, 1913	Esti- mated Heat Pro- duc- tion per 24 Hrs.	Food			Food N., Gm.	Urine N., Gm.	Feces N., Gm.*	Excreta N., Gm.*	Nitrogen Balance, Gm.	Body Weight, Kg.	Urine Volume, Ccs.	Feces Fat
		Total Calories	Carbo- hydrate, Gm.	Fat, Gm.								
Dec. 3	.....	3,189	356.0	141.0	16.0	8.52	2.4	10.9	+5.1	47.31	930	
Dec. 4	.....	3,118	250.0	180.0	16.0	8.70	2.4	11.1	+4.9	.....	1,500	
Dec. 5	.....	2,977	156.0	209.0	15.0	8.74	2.3	11.0	+4.0	.....	1,500	
Dec. 6	.....	2,998	161.0	209.0	15.0	9.75	2.3	12.1	+2.9	46.55	1,340	
Dec. 7	.....	3,097	202.0	221.0	16.0	9.08	2.4	11.5	+4.5	.....	1,640	
Dec. 8	.....	3,014	206.0	289.0	14.9	8.55	2.2	10.8	+4.1	.....	1,340	
Dec. 9	.....	3,689	219.0	290.0	15.2	7.65	2.3	10.0	+5.2	47.53	1,140	
Dec. 10	.....	3,989	219.0	290.0	15.2	8.85	2.3	11.2	+4.0	.....	1,550	
Dec. 11	.....	3,989	219.0	290.0	15.2	9.31	2.3	11.6	+3.6	48.46	1,850	
Dec. 12	1,857	3,552	222.0	226.0	21.3	9.87	3.2	13.1	+8.2	48.64	1,700	
Dec. 13	1,604	2,925	395.0	104.0	13.1	12.64	2.0	14.6	-1.5	48.10	1,935	
Dec. 14	.....	3,256	475.0	95.0	16.5	9.47	2.5	12.0	+4.5	.....	1,100	
Dec. 15	1,723	3,117	511.0	74.0	13.0	8.68	2.0	10.7	+2.3	47.87	1,229	
Dec. 16	1,703	2,132	275.0	76.0	11.6	10.24	1.7	11.9	-0.3	47.91	802	
Dec. 17	.....	3,865	440.0	193.0	15.5	9.30	2.3	11.6	+2.9	.....	1,240	
Dec. 18	.....	3,499	256.0	224.0	14.4	10.82	2.2	13.0	+1.4	.....	1,670	
Dec. 19	2,058	2,565	248.0	173.0	9.6	11.34	1.4	12.7	-3.1	48.34	1,282	
Dec. 20	2,081	2,748	150.0	190.0	14.1	13.41	2.1	15.5	-1.4	48.55	1,343	
Dec. 21	.....	3,426	204.0	232.0	16.0	17.32	2.4	19.7	-3.7	48.55	1,560	
Dec. 22	2,217	3,034	345.0	140.0	12.2	14.42	1.8	16.2	-4.0	48.50	1,223	
Dec. 23	1,962	2,469	121.0	180.0	10.7	11.94	1.6	13.5	-2.8	48.54	883	
Dec. 24	.....	3,657	206.0	225.0	16.5	13.66	2.5	15.6	+0.9	.....	1,480	
Dec. 25	.....	.....	.....	.....	.....	10.90	.....	.....	.....	.....	1,200	
Dec. 26	.....	3,560	189.0	253.0	17.1	10.48	2.6	13.1	+4.0	49.70	1,680	
Dec. 27	.....	3,180	159.0	227.0	16.4	11.10	2.5	13.6	+2.8	.....	1,630	
Dec. 28	.....	3,128	157.0	224.0	16.5	11.43	2.3	13.7	+1.8	.....	1,740	
Dec. 29	.....	3,199	157.0	223.0	16.5	11.77	2.3	14.1	+1.4	.....	1,380	
Dec. 30	.....	3,277	170.0	235.0	15.5	11.72	2.3	14.0	+1.5	.....	1,710	
Dec. 31	.....	2,660	292.0	140.0	17.9	12.61	2.7	15.3	+2.6	.....	1,600	
1914	.....	2,661	256.0	196.0	16.4	12.11	2.3	14.4	+1.0	.....	2,120	
Jan. 1	1,507	2,078	141.0	132.0	10.7	10.01	1.6	11.6	-0.9	49.22	1,330	
Jan. 2	.....	3,651	158.0	216.0	15.6	12.37	2.3	14.6	+1.0	.....	2,160	
Jan. 3	.....	3,070	163.0	216.0	16.7	10.40	2.4	12.8	+2.9	.....	1,750	
Jan. 4	.....	.....	.....	.....	.....	11.21	.....	.....	.....	.....	1,580	
Jan. 5	.....	3,044	153.0	215.0	15.5	12.39	2.3	15.0	+0.5	.....	2,000	
Jan. 6	.....	3,045	153.0	215.0	15.5	11.66	2.3	14.0	+1.5	.....	1,800	
Jan. 7	.....	3,063	162.0	215.6	15.6	11.77	2.3	14.1	+1.5	.....	1,660	
Jan. 8	.....	3,063	162.0	215.6	15.6	11.66	2.3	14.0	+1.6	.....	1,660	
Jan. 9	.....	3,475	268.0	268.0	17.3	10.36	2.6	14.7	+2.6	.....	1,600	
Jan. 10	.....	3,739	354.0	190.0	16.8	12.32	2.6	15.3	+4.6	.....	1,500	
Jan. 11	.....	3,551	344.0	177.0	16.5	13.61	2.6	15.5	+4.9	.....	1,550	
Jan. 12	.....	4,198	382.0	290.0	22.1	11.46	2.3	14.8	-7.2	.....	1,500	

\* Excreta nitrogen estimated as urine nitrogen + 15 per cent of food nitrogen.

TABLE 6.—CLINICAL DATA—(Continued)

HOWARD F.

Date, 1913	Food			Food N., Gm.	Urine N., Gm.	Excreta N., Gm.	Nitrogen Bal., Gm.*	Body Wt., Kg.	Urine Vol., C.c.
	Total Calories	Carbohy- drate, Gm.	Fat, Gm.						
Nov. 6....	1,264	83.0	81.0	6.7	12.83	13.50	-6.80	36.06	970
Nov. 7....	918	62.0	59.0	4.4	12.05	12.49	-8.09	35.74	640
Nov. 8....	1,538	87.0	107.0	7.0	12.75	13.45	-6.45	35.79	840
Nov. 9....	1,454	106.0	88.0	7.7	12.61	13.38	-5.68	.....	760
Nov. 10....	1,401	115.0	78.0	8.1	12.67	13.48	-5.88	.....	680
Nov. 11....	925	93.0	33.0	7.5	13.79	14.54	-7.04	34.60	750
Nov. 12....	950	98.0	40.0	7.3	13.42	14.15	-6.85	35.01	830
Nov. 13....	1,260	134.0	60.0	5.3	12.52	13.10	-7.30	34.22	610
Nov. 14....	580	52.0	30.0	3.4	10.42	10.76	-7.36	.....	500
Nov. 15....	1,152	83.0	69.0	6.6	11.10	11.76	-5.16	33.36	900
Nov. 16....	1,096	150.0	40.0	4.4	9.98	10.42	-6.02	.....	500
Nov. 17....	1,462	123.0	83.0	7.2	9.30	10.02	-2.82	33.12	400
Nov. 18....	1,588	128.0	91.0	8.5	10.20	11.05	-2.55	32.93	590
Nov. 19....	984	63.0	62.0	5.7	10.65	11.22	-5.52	.....	780
Nov. 20....	1,238	74.0	75.0	7.3	10.25	10.98	-3.68	32.57	550
Nov. 21....	1,466	91.0	95.0	8.1	11.32	12.13	-4.03	.....	700
Nov. 22....	1,198	73.0	94.0	8.8	11.12	12.00	-3.20	.....	800
Nov. 23....	1,789	92.0	121.0	11.6	11.15	12.31	-0.71	.....	660
Nov. 24....	1,846	146.0	145.0	10.6	10.82	11.88	-1.28	.....	820
Nov. 25....	2,060	138.0	129.0	11.4	9.81	10.95	+0.45	32.14	940
Nov. 26....	2,686	176.0	168.0	15.7	10.42	11.99	+3.71	.....	780
Nov. 27....	2,240	211.0	118.0	10.9	9.47	10.56	+0.34	.....	570
Nov. 28....	2,742	245.0	145.0	15.0	9.98	11.48	+3.52	32.25	920
Nov. 29....	2,581	211.0	152.0	11.9	8.52	9.71	+2.19	.....	620
Nov. 30....	2,922	273.0	153.0	14.8	9.53	11.01	+3.79	.....	1,220
Dec. 1....	2,581	309.0	112.0	10.6	7.77	8.83	+1.77	.....	870
Dec. 2....	2,298	247.0	110.0	10.0	7.69	8.69	+1.31	33.09	900
Dec. 3....	3,689	423.0	163.0	17.2	9.25	10.97	+6.23	.....	900
Dec. 4....	3,627	441.0	147.0	17.7	9.00	10.77	+6.93	.....	1,130
Dec. 5....	2,671	337.0	81.0	21.0	13.01	15.11	+5.89	34.77	1,500
Dec. 6....	2,476	333.0	83.0	12.9	9.20	10.49	+2.41	33.81	775
Dec. 7....	3,621	496.0	119.0	19.0	10.45	12.35	+6.65	.....	1,500
Dec. 8....	3,391	434.0	112.0	17.8	9.89	11.67	+6.13	.....	1,270
Dec. 9....	3,042	386.0	108.0	18.0	10.73	12.53	+5.47	35.51	1,300
Dec. 10....	2,986	394.0	101.0	16.8	10.51	12.19	+4.61	.....	1,450
Dec. 11....	3,149	405.0	114.0	17.8	10.79	12.57	+5.23	35.99	1,450
Dec. 12....	3,100	417.0	101.0	17.5	10.36	12.11	+5.39	.....	1,610
Dec. 13....	3,544	472.0	122.0	18.5	10.63	11.88	+6.62	36.65	1,280

TABLE 6.—CLINICAL DATA—(Continued)  
HOWARD F.—(Continued)

Date, 1913	Food			Food N., Gm.	Urine N., Gm.	Excreta N., Gm.	Nitrogen Bal., Gm.*	Body Wt., Kg.	Urine Vol., C.c.
	Total Calories	Carbohy- drate, Gm.	Fat, Gm.						
Dec. 14....	3,338	402.0	133.0	17.8	11.01	12.79	+5.01	.....	1,880
Dec. 15....	3,280	510.0	130.0	19.2	12.98	14.90	+4.30	37.54	1,890+
Dec. 16....	3,511	444.0	129.0	19.2	13.23	15.20	+4.00	.....	1,580
Dec. 17....	3,170	345.0	139.0	18.0	9.95	11.75	+6.25	39.10	1,720
Dec. 18....	2,008	248.0	73.0	10.5	8.57	9.62	+0.88	37.17	1,600
Dec. 19....	3,550	411.0	144.0	20.3	11.89	13.92	+6.33	.....	2,050
Dec. 20....	2,671	110.0	197.0	15.0	8.10	9.60	+5.40	.....	1,540
Dec. 21....	2,383	104.0	175.0	12.6	10.65	11.91	+0.69	.....	1,250
Dec. 22....	2,935	159.0	198.0	17.3	13.23	14.96	+2.34	37.21	1,150
Dec. 23....	3,520	239.0	235.0	13.9	9.19	10.58	+3.32	.....	1,200
Dec. 24....	3,605	219.0	243.0	17.4	10.70	12.44	+4.96	.....	1,700
Dec. 25....	.....	.....	.....	.....	10.42	.....	.....	.....	1,370
Dec. 26....	3,152	219.0	199.0	15.6	9.77	11.33	+4.27	39.46	2,100
Dec. 27....	3,303	257.0	196.0	16.8	10.03	11.71	+5.09	.....	1,600
Dec. 28....	2,946	200.0	186.0	15.4	7.51	9.05	+6.35	.....	1,080
Dec. 29....	4,199	265.0	278.0	20.5	10.87	12.92	+7.53	.....	1,640
Dec. 30....	2,325	165.0	145.0	11.4	7.81	8.95	+2.45	39.39	987
Dec. 31....	3,569	317.0	192.0	18.5	11.77	13.62	+4.83	.....	1,500
1914 Jan. 1....	2,912	236.0	169.0	14.5	9.02	10.47	+4.03	.....	1,600
Jan. 2....	2,891	224.0	156.0	16.0	8.74	10.34	+5.66	.....	1,540

\* Excreta nitrogen estimated as urine nitrogen + 10 per cent of food nitrogen.

TABLE 6.—CLINICAL DATA—(Continued)

KARL S.

Date, 1914	Esti- mated Heat Produc- tion per 24 Hrs.	Food			Food N., Gm.	Urine N., Gm.	Feces N., Gm.	Excreta N., Gm.*	Nitrogen Balance, Gm.	Body Weight, Kg.	Urine Volume, C.c.
		Total Calories	Carbo- hydrate, Gm.	Fat, Gm							
Jan. 3	.....	2,038	104.0	145.0	10.8	20.52	...	21.60	-10.80	.....	880
Jan. 4	....	1,801	113.0	71.0	6.9	21.72	...	22.41	-15.51	.....	1,240
Jan. 5	2,579	1,110	95.0	64.0	5.4	.....	...	.....	.....	54.67	725
Jan. 6	2,707	1,332	167.0	32.0	13.6	22.36	...	23.72	-10.12	54.31	1,010
Jan. 7	.....	1,942	93.2	136.0	11.3	.....	...	.....	.....	.....	810
Jan. 8	.....	2,331	136.0	156.0	12.5	16.03	...	17.28	-4.78	.....	860
Jan. 9	.....	1,892	114.0	126.0	9.8	23.84	...	24.82	-15.02	52.99	1,700
Jan. 10	.....	2,910	223.0	174.0	14.6	.....	...	.....	.....	.....	.....
Jan. 11	.....	3,018	318.0	139.0	16.4	.....	...	.....	.....	.....	.....
Jan. 12	.....	3,017	322.0	138.0	16.2	18.15	1.6	19.8	-3.6	.....	2,310
Jan. 13	.....	2,966	326.0	128.0	17.2	13.94	1.7	15.6	+1.6	.....	1,820
Jan. 14	....	2,802	313.0	118.0	16.4	17.06	1.6	18.7	-2.3	.....	1,830
Jan. 15	.....	3,129	323.0	149.0	16.2	18.65	1.6	20.3	-4.1	52.74	1,920
Jan. 16	2,203	2,448	226.0	132.0	11.5	19.11	1.2	20.3	-8.8	52.24	1,960
Jan. 17	.....	3,398	340.0	166.0	17.9	19.16	1.8	21.0	-3.1	.....	1,940
Jan. 18	.....	3,138	329.0	145.0	17.1	17.26	1.7	19.0	-1.9	.....	1,920
Jan. 19	1,651	2,795	268.0	145.0	13.6	14.72	1.4	16.1	-2.5	51.21	1,260
Jan. 20	.....	2,965	313.0	138.0	15.7	14.51	1.6	16.1	-0.4	.....	1,550
Jan. 21	1,798	2,912	315.0	129.0	16.3	17.57	1.6	19.2	-2.9	51.52	1,870
Jan. 22	1,512	2,605	253.0	133.0	12.8	13.25	1.3	14.6	-1.8	51.18	1,194
Jan. 23	.....	3,033	324.0	140.0	15.9	11.99	1.6	13.6	+2.3	.....	1,360
Jan. 24	.....	2,982	315.0	138.0	15.8	13.06	1.6	14.7	+1.1	.....	1,960
Jan. 25	.....	2,987	315.0	139.0	15.8	13.17	1.6	14.8	+1.0	.....	1,400
Jan. 26	.....	3,541	408.0	155.0	16.7	12.64	1.7	14.3	+2.4	54.84	1,620
Jan. 27	.....	3,999	439.0	191.0	16.3	13.06	1.6	14.7	+1.6	.....	1,460
Jan. 28	.....	4,025	439.0	194.0	16.3	11.88	1.6	13.5	+2.8	.....	1,280
Jan. 29	.....	3,975	438.0	190.0	16.1	11.32	1.6	12.9	+3.2	52.54	1,450
Jan. 30	.....	3,991	439.0	191.0	16.2	10.65	1.6	12.3	+3.9	.....	1,500
Jan. 31	.....	3,922	418.0	193.0	16.2	10.93	1.6	12.5	+3.7	.....	1,400
Feb. 1	.....	3,940	418.0	194.0	16.3	10.63	1.6	12.2	+4.1	.....	1,500
Feb. 2	.....	3,808	419.0	180.0	16.0	11.21	1.6	12.8	+3.2	.....	1,910
Feb. 3	....	3,808	419.0	180.0	16.0	11.15	1.6	12.8	+3.2	.....	1,980
Feb. 4	....	3,971	442.0	188.0	16.0	10.87	1.6	12.5	+3.5	.....	1,870
Feb. 5	.....	3,974	438.0	191.0	16.0	9.29	1.6	10.9	+5.1	.....	1,640
Feb. 6	1,916	3,232	330.0	165.0	13.3	10.24	1.3	11.5	+1.8	53.33	1,360
Feb. 7	1,965	3,526	387.0	148.0	22.1	.....	2.2	17.3	+4.8	54.48	2,300
Feb. 8	.....	4,018	474.0	178.0	16.3	11.67	1.6	13.3	+3.0	.....	1,440

\* Excreta nitrogen estimated as urine nitrogen + 10 per cent. of food nitrogen.

Date 1913	Temperature		Food			Food N., Gm.	Urine N., Gm.	Feces N., Gm.	Excreta N., Gm.	Nitrogen Balance, Gm.	Body Weight, Kg.	Urine Volume, C.c.	Feces Fat
			Total Calories	Carbo- hy- drate, Gm.	Fat, Gm.								
	Max.	Min.											
Oct. 7	103.0	101.4	3,052	168.0	212.0	15.0	24.55	2.09	26.64	-11.64	76.08	1,240	9.19
Oct. 8	103.6	101.2	3,010	163.0	210.0	15.0	25.50	2.09	27.59	-12.59	75.61	1,270	9.19
Oct. 9	104.0	101.6	3,010	163.0	210.0	15.0	21.29	2.09	23.38	-8.38	75.73	1,120	9.19
Oct. 10	103.6	101.6	3,030	163.0	212.0	15.0	23.67	2.09	25.76	-10.76	76.02	1,740	9.19
Oct. 11	103.0	101.0	3,014	479.0	71.0	14.9	20.12	1.89	22.01	-7.11	74.85	1,500	5.80
Oct. 12	102.8	101.6	3,018	480.0	71.0	15.0	17.77	1.89	19.66	-4.66	.....	1,960	5.80
Oct. 13	102.4	100.6	3,014	479.0	71.0	14.9	18.77	1.89	20.66	-5.76	74.24	1,980	5.80
Oct. 14	103.0	100.0	3,045	173.0	212.0	14.2	18.21	1.23	19.49	-5.29	74.38	1,220	5.02
Oct. 15	102.2	98.6	2,570	130.0	187.0	11.7	18.61	1.23	19.89	-8.19	.....	1,040	5.02
Oct. 16	101.0	99.4	3,058	168.0	212.0	15.4	21.04	1.23	22.32	-6.92	.....	1,010	5.02
Oct. 17	101.6	99.4	3,211	484.0	78.0	15.6	17.79	...	19.35*	-3.75	73.10	1,120	
Oct. 18	100.6	99.0	2,998	476.0	71.0	15.0	15.69	....	17.19	-2.19	.....	1,100	
Oct. 19	99.6	98.6	3,019	481.0	71.0	15.0	15.30	....	16.80	-1.80	.....	1,220	
Oct. 20	99.6	98.6	3,002	468.0	75.0	15.0	15.24	....	16.74	-1.74	72.82	1,880	
Oct. 21	98.6	99.4	2,675	412.0	68.0	13.0	15.75†	....	.....	.....	.....	1,610+ (?)	
Oct. 22	99.6	98.8	2,943	462.0	71.0	15.0	16.32	....	17.82	-2.82	.....	1,480	
Oct. 23	99.6	98.6	3,062	449.0	76.0	21.2	16.76	....	18.88	+2.32	.....	1,230	
Oct. 24	99.6	98.6	3,396	541.0	60.0	20.0	13.34	...	15.34	+4.66	72.86	1,640	
Oct. 25	99.6	98.6	3,211	493.0	71.0	20.0	16.59	....	18.59	+1.41	.....	1,120	
Oct. 26	99.0	98.2	3,066	164.0	215.0	15.5	18.90	....	20.45	-4.95	.....	1,320	
Oct. 27	99.6	98.4	3,159	164.0	219.0	17.5	17.65	....	19.40	-1.90	.....	2,280	
Oct. 28	99.0	98.2	3,277	182.0	220.0	18.5	14.18	....	16.03	+2.47	73.09	1,220	

† This is the total for 19½ hours.

\* Excreta nitrogen estimated as urine nitrogen + 10 per cent. of food nitrogen.

TABLE 6.—CLINICAL DATA—(Continued)

RICHARD T.

Date 1913	Temperature		Food			Food N., Gm.	Urine N., Gm.	Feces N., Gm.	Excreta N., Gm.	Nitrogen Balance, Gm.	Body Weight, Kg.	Urine Volume, C.c.	Feces Fat
			Total Calories	Carbo- hy- drate, Gm.	Fat, Gm.								
	Max.	Min.											
Oct. 17	103.6	101.4	1,656	243.0	33.0	11.3	13.95	0.84	14.79	-3.49	26.09	2,290	1.63
Oct. 18	104.2	100.8	1,143	115.0	49.0	8.4	12.48	0.84	13.32	-4.92	.....	1,145	1.63
Oct. 19	103.2	100.8	2,131	327.0	49.0	13.0	14.40	0.84	15.24	-2.24	.....	1,720	1.63
Oct. 20	104.0	100.0	2,020	280.0	55.0	14.0	14.53	0.84	15.37	-1.37	.....	1,005	1.63
Oct. 21	102.8	100.0	2,359	360.0	51.0	16.0	15.13	0.84	15.97	+0.03	.....	1,320	1.63
Oct. 22	102.4	99.4	2,092	315.0	46.0	14.7	14.74	0.84	15.58	-0.88	35.57	1,200	1.63
Oct. 23	103.0	99.0	2,576	369.0	67.0	17.4	16.30	0.84	17.14	+0.26	35.70	1,570	1.63
Oct. 24	102.0	99.4	2,153	333.0	35.0	18.0	15.69	0.84	16.53	+1.47	.....	1,340	1.63
Oct. 25	101.0	98.4	2,519	228.0	125.0	16.0	16.32	0.84	17.16	-1.16	.....	1,390	1.63
Oct. 26	100.6	99.0	2,093	115.0	133.0	15.0	16.53	.....	18.03	-3.03	.....	1,100	
Oct. 27	100.2	98.6	2,163	121.0	139.0	16.7	16.34	.....	17.91	-2.21	35.30	1,200	
Oct. 28	99.6	98.6	2,009	124.0	117.0	16.0	16.47	.....	18.07	-2.07	35.60	1,460	
Oct. 29	100.0	98.6	3,276	343.0	157.0	15.2	14.01	.....	15.53	-0.33	.....	1,370	
Oct. 30	100.0	99.0	2,969	302.0	144.0	15.1	11.77	.....	13.23	+1.82	35.28	1,195	
Oct. 31	101.6	99.2	2,954	310.0	142.0	15.5	12.05	.....	13.60	+1.90	.....	1,420	
Nov. 1	102.0	100.4	3,069	334.0	142.0	14.5	11.32	.....	12.77	+1.73	35.38	1,320	
Nov. 2	102.4	99.6	2,995	325.0	138.0	14.5	11.74	.....	13.19	+1.31	.....	1,900	
Nov. 3	101.0	99.6	2,984	316.0	140.0	15.1	11.99	.....	13.50	+1.60	36.27	1,270	
									13.74	+1.46	36.42	1,560	

TABLE 6.—CLINICAL DATA—(Continued)  
EDWARD B.

Date, 1914	Esti- mated Heat Production per 24 Hrs.	Food			Food N., Gm.	Urine N., Gm.	Excreta N., Gm.*	Nitrogen Balance Gm.	Body Weight, Kg.	Urine Volume, C.c.
		Total Calories	Carbo- hydrate, Gm.	Fat, Gm.						
Oct. 14	.....	3,901	214.9	284.8	14.5	14.51	15.96	-1.46	56.29	1,180
Oct. 15	.....	4,171	212.9	309.3	16.4	11.39	13.03	+3.4	.....	1,415
Oct. 16	.....	4,008	662.0	97.2	15.0	11.49	12.99	+2.0	56.36	1,665(?)
Oct. 17	.....	1,561	286.3	43.8	7.28	8.65	9.37	-2.09	56.94	1,140
Oct. 18	.....	2,976	94.5	236.9	15.0	11.08	12.58	-2.42	56.01	1,690
Oct. 19	.....	4,217	111.0	362.1	13.9	16.17	17.56	-3.66	56.98	2,230
Oct. 20	.....	4,097	114.9	348.9	14.80	10.96	12.44	+2.36	56.57	1,520
Oct. 21	.....	3,586	518.9	114.7	15.20	9.17	10.69	+4.51	57.21	1,250
Oct. 22	.....	3,076	579.6	54.2	7.68	7.55	8.61	-0.93	56.60	1,170
Oct. 23	2,160	3,462	152.8	269.1	12.90	8.21	9.50	+3.40	55.76	835
Oct. 24	.....	4,072	220.6	299.4	15.0	11.94	13.44	+1.56	56.84	1,465
Oct. 25	.....	4,114	220.9	303.1	15.1	11.20	12.70	+2.40	56.73	1,515
Oct. 26	1,976	2,704	151.4	124.1	6.9	6.75	7.44	-0.54	.....	663
Oct. 27	1,982	3,844	109.1	334.5	11.1	8.61	9.72	+1.88	.....	1,125
Oct. 28	.....	4,056	223.4	295.7	15.2	8.19	9.71	+5.49	57.51	2,155
Oct. 29	.....	4,185	314.8	265.7	16.5	8.70	10.35	+6.15	57.46	1,960
Oct. 30	.....	3,643	364.7	179.0	18.8	10.30	12.18	+6.62	57.83	2,310
Oct. 31	.....	3,893	402.5	191.4	18.0	9.72	11.62	+6.48	.....	1,655
Nov. 1	.....	4,394	455.7	218.4	19.3	11.05	12.98	+6.82	58.53	2,450
Nov. 2	.....	4,491	451.6	225.8	21.0	11.80	13.9	+7.1	58.76	1,770
Nov. 3	.....	4,836	491.9	244.6	21.2	12.20	14.32	+6.88	59.52	2,405
Nov. 4	1,936	2,209	209.4	119.7	9.2	9.20	10.12	-0.92	.....	979
Nov. 5	.....	3,960	390.5	195.9	17.0	10.59	12.29	+5.71	.....	1,665
Nov. 6	2,117	1,907	219.5	85.9	8.0	10.96	11.76	-3.76	.....	1,523
Nov. 7	.....	1,006	101.2	49.8	5.05	12.13	12.63	-7.58	59.28	1,075
Nov. 8	.....	398	64.0	11.8	1.08	10.34	10.44	-9.36	.....	665
Nov. 9	.....	617	94.8	20.0	1.08	11.26	11.42	-9.74	57.06	645
Nov. 10	2,632	1,103	104.3	51.2	6.0	14.72	15.32	-9.32	.....	833
Nov. 11	.....	1,646	96.0	84.2	9.7	16.73	17.70	-8.0	57.11	1,230
Nov. 12	.....	2,196	165.9	119.3	10.7	14.79	15.8	-5.1	.....	1,250

\* Excreta nitrogen estimated as urine nitrogen + 10 per cent. of food nitrogen.

TABLE 6.—CLINICAL DATA—(Continued)  
JOHN K.

Date, 1913	Total Calories	Carbohy- drate, Gm.	Fat, Gm.	Food N., Gm.	Urine N., Gm.	Excreta N., Gm.	Nitrogen Bal., Gm.	Body Wt., Kg.	Urine Vol., C.c.
Dec. 15	* 2,194	139.1	148.9	9.3	24.58	25.51	-16.21	63.81	1,152
Dec. 16	3,309	145.1	246.8	16.3	21.45	23.08	-6.78	63.55	1,180
Dec. 17	3,521	161.9	258.1	14.6	22.37	23.83	-9.23	63.27	3,110
Dec. 18	3,205	161.9	223.6	14.8	19.30	20.78	-5.98	63.35	3,040
Dec. 19	3,788	251.6	249.6	17.0	19.40	21.10	-4.10	63.05	3,230
Dec. 20	3,916	259.7	257.1	18.0	18.26	20.06	-2.06	62.37	3,460
Dec. 21	4,134	342.5	238.4	20.0	19.33	21.33	-1.33	63.04	4,285
Dec. 22	4,558	378.4	267.2	20.4	18.00	20.04	+0.36	62.64	4,255
Dec. 23	4,838	393.9	285.8	22.0	17.93	22.13	-0.13	63.26	3,210
Dec. 24	4,450	373.1	259.1	19.9	18.76	20.77	-0.87	63.32	3,350

\* Estimated heat production, 2,568 calories.



Subject and Date	Character of Experiment	Period of Disease	Aver. age Rectal Temp. C.	Aver. age Pulse Rate	Aver. age Respiratory Quotient	Indirect Calorimetry		Per Cent. Excess of Direct Cal.		Per Cent. Rise Above Normal Patient's Own Basal Metabolism	Day of Basal Determination Used for Comparison
						Cal. per kg. per Set M.	Cal. per Hour	According to Rectal Temp.	According to Indirect Calories		
Morris S. 25	9.9 gm. N	Continued temperature	40.0	99	.77	1.70	51.42	- 5	.....	+ .48	
Oct 24, 1914	Basal.....	Continued temperature	39.5	101	.84	1.70	51.27	- 2	.....	.....	Oct. 24.
28	115.0 gm glucose	Continued temperature	39.2	111	.62	1.64	49.35	+ 1	.....	.....	Oct. 29.
29	Basal.....	Continued temperature	39.6	106	.79	1.62	49.04	- 1	.....	+ .11	
31	10.3 gm N	Early steep curve.....	39.1	100	.81	1.68	50.21	- 11	.....	.....	Oct. 29.
Nov 2	Restless	Early steep curve.....	38.9	103	.80	1.66	49.46	- 9	.....	+ .43	
5	Basal.....	Early steep curve.....	38.1	105	.81	1.60	47.31	- 4	.....	+ .36	
17	Basal.....	First Release Ascending temperature	38.7	103	.81	1.44	42.52	- 1	+ 1	+ .33	
18	Basal.....	Ascending temperature	39.9	113	.83	1.62	45.38	+ 1	- 1	+ .21	
21	Basal.....	Continued temperature	39.4	124	.76	1.70	52.69	- 17	.....	+ .52	
25	8.7 gm. N	Continued temperature	39.2	113	.81	1.84	54.17	- 8	.....	.....	Av. Nov. 24 and 26.
26	Basal.....	Early steep curve.....	39.1	113	.76	1.78	51.60	- 17	.....	+ .49	
Dec 17	10.6 gm N	7th day, normal temp	37.0	94	.84	1.45	42.89	- 9	- 8	.....	Dec. 13.
13	Basal.....	8th day, normal temp.	37.0	83	.82	1.33	36.33	+ 0	+ 4	+ 5	
15	115 gm glucose	10th day, normal temp	37.2	95	1.01	1.36	40.07	- 8	- 11	.....	Dec. 16.
16	Basal.....	11th day, normal temp.	37.3	88	.88	1.31	38.67	2	+ 0	+ 11	
19	115 gm glucose	Second Release Ascending temperature	39.4	116	.93	1.66	47.46	+ 2	- 4	.....	Dec. 30.
20	Basal.....	Early steep curve.....	39.6	113	.78	1.61	46.83	- 1	- 2	+ .35	
22	115 gm glucose	Early steep curve.....	39.2	116	.94	1.55	46.01	+ 11	+ 10	.....	Av. Dec. 30 and 31.
23	Basal.....	Early steep curve.....	38.3	101	.79	1.50	44.57	+ 5	+ 2	+ .28	
Jan. 2, 1914	Basal.....	8th day, normal temp.	37.0	75	.81	1.17	34.93	+ 3	+ 5	+ 1	
27	Basal.....	29th day, normal temp.	36.9	66	.82	1.10	31.30	+ 7	+ 4	- 1	
Dec 17, 1914	Basal.....	One year later.....	36.8	62	.81	1.10	35.16	+ 0	.....	+ 1	
18	9.6 gm. N	One year later.....	36.9	68	.88	1.16	37.44	+ 4	.....	.....	Dec. 17, 1914.

TABLE 7.—SUMMARY OF CLINICAL CALORIMETRY IN TYPHOID FEVER—(Continued)

Subject and Date	Character of Experiment	Period of Disease	Aver. age Rectal Temp. C.	Aver. age Pulse Rate	Aver. age Respiratory Quotient	Indirect Calorimetry Average per Hour		Per Cent. Divergence of Direct Cal. from Indirect Calories		Per Cent. Rise Above Normal Patient's Own Basal Metabolism	Day of Basal Determination (used for Comparison)
						Cal. per Kg.	Cal. per Sq. M.	Accord- ing to Rectal Temp.	Accord- ing to Surface Temp.		
Charles F. Nov. 10, 1913											
	Basal.....	Ascending temperature	39.1	78	.79	1.44	45.26	- 7	- 6	+30	
11	6.6 gm. N.....	Ascending temperature	39.2	82	.84	1.50	47.28	+ 1	- 2	....	Nov. 10, 1913.
14	115 gm. glucose.....	Continued temperature	39.5	97	.90	1.54	48.12	- 8	- 6	....	Nov. 15.
15	Basal.....	Continued temperature	39.9	89	.78	1.52	47.49	-10	- 9	+27	
29	Basal.....	Early steep curve.....	36.9	83	.82	1.29	38.54	+ 2	.....	+11	
Dec. 8	10.5 gm. N.....	7th day, normal temp.	36.8	77	.92	1.38	41.53	- 3	.....	....	Dec. 9.
9	Basal.....	8th day, normal temp.	36.8	78	.92	1.20	35.96	+ 3	.....	+ 4	
10	115 gm. glucose.....	9th day, normal temp.	36.7	80	1.00	1.33	40.18	-10	.....	....	Dec. 9.
26	Basal.....	25th day, normal temp.	36.9	76	.85	1.17	36.36	+ 8	+ 1	+ 5	
31	Basal.....	30th day, normal temp.	37.0	80	.79	1.21	37.52	- 5	- 8	+ 8	
Howard F. Nov. 7, 1914											
	Basal.....	Ascending temperature	39.7	103	.78	1.85	49.93	-10	- 3	+44	
12	6.5 gm. N.....	Continued temperature	39.9	105	.81	1.93	51.15	- 2	+ 1	....	Nov. 13.
13	Basal.....	Continued temperature	39.8	107	.78	1.78	47.00	- 2	- 2	+35	
20	Basal.....	Continued temperature	39.2	99	.76	1.76	45.52	- 2	- 0	+31	
Dec. 1	115 gm. glucose.....	5th day, normal temp.	37.0	97	.97	1.54	40.10	- 8	.....	....	Dec. 2.
2	Basal.....	6th day, normal temp.	36.9	76	.94	1.35	35.15	+ 6	.....	+ 1	
5	10.2 gm. N.....	9th day, normal temp.	37.1	91	.85	1.79	47.25	- 2	.....	....	Dec. 6.
6	Basal.....	10th day, normal temp.	37.0	75	.96	1.45	38.03	+ 0	.....	+10	
18	Basal.....	22d day,* normal temp.	37.2	107	.84	1.60	43.28	+ 1	+ 1	+25	
30	Basal.....	34th day,* normal temp.	37.2	108	.82	1.52	42.08	- 2	+	+21	

Karl S. Jan. 3, 1914	Basal.....	Continued temperature	29.9	112	76	1.71	54.01	- 3	- 6	+56	
6	10 gm. N.....	Continued temperature	29.9	108	82	1.89	57.02	+ 3	+ 6	....	+ 7.3
9	Basal.....	Late steep curve	28.9	95	79	1.57	46.76	....	....	+35	
19	Basal.....	1st day, normal temp.	29.0	77	88	1.19	35.83	....	....	+ 3	
31	100 gm. N.....	3d day, normal temp.	30.5	72	90	1.66	40.06	....	....	....	+21.1
22	Basal.....	4th day, normal temp.	30.9	61	89	1.10	33.03	....	....	- 5	
Feb. 6	Basal.....	18th day, normal temp.	30.9	81	81	1.23	40.51	- 8	- 6	+17	
7	9.6 gm. N.....	19th day, normal temp.	31.0	80	80	1.35	42.08	- 5	+ 2	....	+ 3.9
Thomas B. Oct. 13, 1913	Basal.....	Late steep curve.....	35.1	85	82	1.05	36.51	- 6	....	+ 5	
31	Basal.....	1st day, normal temp.	36.9	78	92	0.93	31.57	+ 2	....	- 9	
Richard T. Oct. 18, 1913	Basal.....	Early steep curve.....	36.0	90	81	1.60	45.11	- 4	....	+31	
30	Basal.....	Early steep curve.....	35.2	93	85	1.62	40.92	- 5	....	+25	
Anton K. Oct. 16, 1913	Basal.....	Late steep curve.....	35.1	79	86	1.25	38.26	+ 5	....	+10	
Rose G. Nov. 20, 1913	Basal.....	25th day, normal temp.	35.1	78	87	1.71	43.13	+ 1	....	+24	
Edward F. Oct. 25, 1914	Basal.....	First relapse, early steep curve	38.5	116	79	1.13	44.33	7	....	+58	
26	70 gm. olive oil.....	First relapse; late steep curve	37.9	118	81	1.33	41.50	- 2	....	....	
27	Basal.....	First relapse; late steep curve	37.6	107	79	1.29	40.15	- 7	....	+16	
Nov. 1	Basal.....	4th day, normal temp.	37.2	104	85	1.22	38.39	- 3	....	+12	
6	Basal.....	Second relapse; ascending temp.	39.3	124	82	1.31	41.47	- 5	....	+20	
10	Basal (irrational)	Second relapse; continued temp.	40.3	141	76	1.65	52.18	- 6	....	+50	
John K. Dec. 15, 1914	Basal.....	Continued temperature	39.2	63	77	1.49	48.18	- 4	....	+39	

\* Calculated from averages on account of rapid, irregular and weak heart action.

Oct. 27.

+ 3.1

amounts of heat. Therefore the law of the conservation of energy applies to fever patients.

The rectal temperature does not always give an accurate indication of the average change in body temperature, and better results are often obtained by well covered surface thermometers.

The basal heat production rises and falls in a curve roughly parallel with the temperature. At the height of the fever it averages about 40 per cent. above the normal but in some cases rises to more than 50 per cent. above the normal.

The specific dynamic action of protein and carbohydrate is much smaller in the febrile period of typhoid than in health and in some cases seems to be absent. In convalescence it may be greater than normal.

In a majority of cases a rise in temperature is accompanied by an increasing heat production and an increasing heat elimination.

Typhoid patients can store body fat on an abundant diet while losing body weight and body protein. Loss in weight and loss of protein are usually though not necessarily parallel.

There is a toxic destruction of protein in typhoid fever. This is shown by the fact that patients have a distinctly negative nitrogen balance on a diet which contains more than enough calories to cover the heat production.

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477 First Avenue.

# CLINICAL CALORIMETRY

EIGHTH PAPER

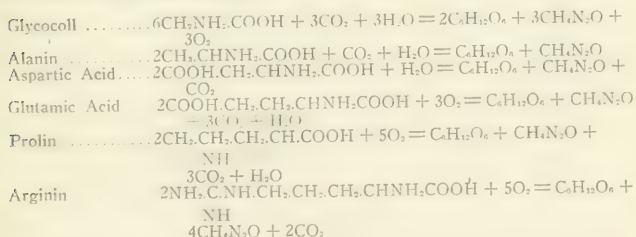
## ON THE DIABETIC RESPIRATORY QUOTIENT\*

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The respiratory quotient, or the ratio of the volume of carbon dioxide expired to the volume of oxygen inspired, in the case of protein oxidation is stated by Loewy<sup>1</sup> to be 0.801. This relation depends on the net result of the oxidation of the many amino-acids of which protein is composed. It is apparent that when some of these amino-acids are converted into glucose which is eliminated in the urine, the respiratory quotient for protein will not hold true. It has been shown<sup>2</sup> that the carbon of glycocoll and alanin is completely converted into glucose in the diabetic organism, and that three of the carbon atoms which are contained in aspartic and glutamic acids are similarly convertible into glucose. Dakin<sup>3</sup> states that prolin and arginin yield glucose comparable in quantity to that yielded by glutamic acid. According to this author cystin and serin also yield glucose.

The reactions involving the conversion of amino-acids into sugar and urea may thus be written:<sup>4</sup>



Osborne and Jones<sup>5</sup> have reported an analysis of 100 grams of ox meat containing 16.18 per cent. of total nitrogen. This analysis will

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1. Loewy: Handb. d. Biochem., 1911, iv, No. 1, 279.

2. Ringer and Lusk: Ztschr. f. physiol. Chem., 1910, lxxvi, 106.

3. Dakin: Jour. Biol. Chem., 1913, xiv, 321.

4. For more complete theoretical details consult: Lusk, Jour. Am. Chem. Soc., 1910, xxxii, 671; and Dakin and Dudley, Proc. Seventeenth Internat. Cong. Med., 1914, Sec. ii, Part II, 127.

5. Osborne and Jones: Am. Jour. Physiol., 1909, xxiv, 438.

be found below together with the respiratory quotients, both normal and diabetic, of the individual amino-acids.

TABLE 1.—ANALYSIS OF 100 GRAMS OX MEAT WITH RESPIRATORY QUOTIENTS

Substance	In 100 Gm. Meat gm.	Respiratory Quotient	
		Normal	Diabetic
Glycocoll .....	2.06	1.00	*
Alanin .....	3.72	0.83	*
Valin .....	0.81	0.75	
Leucin .....	11.65	0.73	
Prolin .....	5.82	0.82	0.60
Phenylalanin .....	3.15	0.87	
Aspartic acid .....	4.51	1.17	†
Glutamic acid .....	15.49	1.00	1.00
Serin .....	?	....	
Tyrosin .....	2.20	0.89	
Arginin .....	7.47	0.73	0.40
Histidin .....	1.76	0.90	
Lysin .....	7.59	0.71	
Ammonia .....	1.07		
Tryptophan .....	Present	0.87	
Total .....	67.30		

\* R. Q. depressed below that of fat if glycocoll or alanin be ingested.

† R. Q. increased above that of fat if aspartic acid be given.

A glance at the above table shows how the respiratory quotient of 0.801 for protein is based on the sum of the results of the oxidation of many different substances, and also that the respiratory quotients usually tend to fall when certain of the amino-acids are converted into sugar.

A clear idea of this fall in the respiratory quotient can only be obtained if the respiratory metabolism of those amino-acids which are convertible into glucose is contrasted, the normal with the diabetic condition.

It will be noted in the foregoing table that only 67 per cent. of the ox protein was recovered as amino-acids. This is explained by the deficiency in the method; for Osborne and Jones<sup>6</sup> have analyzed a specially prepared mixture containing known quantities of a large number of amino-acids and have recovered only 66 per cent. of the substances present. As regards those amino-acids which are convertible into glucose, the following percentages were recovered from the mixture: Alanin, 46 per cent., prolin 73 per cent., aspartic acid, 42.5 per cent., glutamic acid 69 per cent., arginin 65 per cent. If one assumes that the quantity of glycocoll is at least double that found,

6. Osborne and Jones: *Am. Jour. Physiol.*, 1910, xxvi, 325.



one arrives at values from which one may compute the quantity of sugar which should in theory arise from these acids. This appears in Table 2.

Since the 100 gm. of the ox muscle analyzed contained 16.18 gm. of nitrogen, the D:N equals 2.75:1.

TABLE 2.—CALCULATION SHOWING THE ORIGIN OF GLUCOSE FROM PROTEIN

Substance	Osborne	Recalculated	Glucose
Glycocoll . . . . .	2.06	4.0	3.2
Alanin . . . . .	3.72	8.1	8.2
Aspartic acid . . . .	4.51	10.6	7.2
Glutamic acid . . . .	15.49	22.3	13.6
Prolin . . . . .	5.82	8.0	6.3
Arginin . . . . .	7.47	11.5	5.9
		64.5	44.4

TABLE 3.—RESPIRATORY EXCHANGE IN THE NORMAL AND DIABETIC CONDITION OF SIX AMINO-ACIDS, AS THEY ARE CONTAINED IN 100 GM. OF OX MEAT, AND WHICH ARE CONVERTIBLE INTO 44.4 GM. OF GLUCOSE, D:N = 2.75

Substance	Grams	Normal		Diabetic			
		Oxygen gm.	Carbon Dioxid gm.	Oxygen		Carbon Dioxid	
				Absorbed gm.	Eliminated in Reaction gm.	Absorbed in Reaction gm.	Eliminated gm.
Glycocoll . . .	4.0	2.56	3.52		0.85	1.17	
Alanin . . . .	8.1	8.75	10.01	0.0		2.00	
Aspartic acid .	10.6	7.65	12.27	0.0			1.75
Glutamic acid .	22.3	21.85	30.04	7.30			10.03
Prolin . . . .	8.0	12.25	13.77	5.57			4.59
Arginin . . . .	11.5	11.63	11.63	5.32			2.91
				18.19	0.85	3.17	19.28
				0.85			3.17
	64.5	64.69	81.24	17.34			16.11
R. Q			0.915			0.675	

When the D:N ratio is 3.65, 59 gm. of glucose, or 14.6 gm. more than the quantity above estimated, are eliminated in the urine when 100 gm. of protein are destroyed. These 14.6 gm. represent an additional amount of glucose whose origin is unexplained and which is equal to 24 per cent. of the total maximal production. Such sources of sugar might be cystin, which if all the sulphur in protein were in that form

might at most yield 2 gm. of glucose and serin whose solubility has prevented any accuracy of determination.

Having determined the approximate quantities of the various sugar yielding amino-acids, one may now compute the difference between their oxidation normally and in the diabetic. This is shown in Table 3.

This table signifies that when glycocoll, alanin, aspartic acid, glutamic acid, prolin and arginin, together aggregating nearly two-thirds by weight of the protein complex, are oxidized in the normal organism in the proportion in which they may exist in meat, the respiratory quotient is 0.915, whereas if 44.4 gm. of glucose is formed from them the respiratory quotient sinks to only 0.675.

Of those amino-acids which do not yield glucose, three, valin, leucin and lysin, which together aggregate 20 gm. according to Osborne's (uncorrected) analysis of 100 gm. of meat, have respiratory quotients of 0.75, 0.73 and 0.71, respectively, whereas three others, phenylalanin, tyrosin and histidin, together amounting to only 7.1 gm., yield respiratory quotients of 0.87, 0.89 and 0.90. Furthermore, the 1.07 gm. of ammonia liberated would tend to reduce the quotient through urea formation. It is therefore obvious that the respiratory quotient for protein in diabetes is made up predominately of the oxidation of the remnants of the sugar forming amino-acids and from the oxidation of other amino-acids having in the main respiratory quotients of 0.75 to 0.71. As actually calculated, the above named mixture of non-sugar producing amino-acids would yield 48.25 gm. of  $\text{CO}_2$  and require 45.86 gm. of oxygen for oxidation, showing a respiratory quotient of 0.76.

The aggregate quotient of the non-sugar forming amino-acids as set forth above may be indirectly obtained by deducting the estimated respiratory exchange of the sugar-forming amino-acids from that of the total involved in the normal oxidation of 100 gm. of ox protein, as shown in Table 4.

TABLE 4.—AGGREGATE QUOTIENT OF NON-SUGAR FORMING AMINO-ACIDS

	Oxygen gm.	Carbon Dioxid gm.	Resp. Quot.
Normal oxidation of 100 grams of beef protein	138.18	152.17	0.801
Estimated oxidation of the sugar forming amino-acids . . . . .	64.69	81.24	0.915
	73.49	70.93	
Add $\text{CO}_2$ for urea formation from 1.07 gm. $\text{NH}_3$	.....	1.39	
Estimated oxidation of non-sugar forming amino-acids . . . . .	73.49	72.32	0.716

Although the last respiratory quotient 0.716 closely approximates that of leucin (0.73) and lysin (0.71), the dominant non-sugar forming amino-acids, it is evident that the influence of the other non-sugar

forming amino-acids would tend to raise the quotient to a higher level, to 0.76 in the before mentioned calculation. Therefore, the present figures can only be regarded as an attempted solution of the problem rather than as a precise analysis.

When the mixture of six sugar-forming amino-acids, aggregating 64.5 gm., is normally oxidized

$$O_2 = 64.69 \text{ gm. and } CO_2 = 81.24 \text{ gm.}$$

and when it is converted into 44.4 gm. of glucose

$$O_2 = 17.34 \text{ gm. and } CO_2 = 16.11 \text{ gm.}$$

the difference between these two sets of figures will represent the quantities of respiratory gases which would not be involved in the respiratory exchange in diabetes and would amount to

$$O_2 = 47.35 \text{ gm. and } CO_2 = 65.13 \text{ gm.}$$

If one takes the grams of respired gases in the normal combustion of 100 grams of protein as given by Loewy, and deducts from these the quantity not eliminated according to the above computation, one arrives at the following results for the diabetic respiratory quotient:

TABLE 5.—PROTEIN RESPIRATORY QUOTIENT WITH D:N = 2.75

	Oxygen gm.	Carbon Dioxid gm.
Normal oxidation 100 grams beef protein	138.18	152.17
Deduct for intermediary production of 44.4 grams of glucose	47.35	65.13
	<hr/> 90.83	<hr/> 87.04

$$R. Q. = 0.697.$$

Proceeding now to the consideration of the cases of diabetes in which the D:N is 3.65, calculations have been made the relations of which may be thus presented:

TABLE 6.—PROTEIN RESPIRATORY QUOTIENT WITH D:N = 3.65

	Oxygen gm.	Carbon Dioxid gm.
(1). Normal oxidation of 100 grams of beef protein	138.18	152.17
Deduction, if 16.28 grams N $\times$ 3.65 = 59.41 glucose	63.38	87.15
	<hr/> 74.80	<hr/> 65.02

$$R. Q. = 0.632.$$

The respiratory quotient for fat is 0.707, and since fat forms the main recourse of the diabetic, the respiratory quotient will be found nearer to that of fat than to 0.632 for protein. Thus, in a diabetic dog with a D:N ratio of 3.54 in which 23 per cent. of the total heat production was derived from protein and 77 per cent. from fat, the

respiratory quotient was 0.687, the non-protein respiratory quotient being 0.704, which closely approximates that of fat. In the case of a diabetic patient with a low protein metabolism whose urinary D:N was 3.6, Du Bois has found during a three hour period a respiratory quotient of 0.697. In another diabetic man with approximately the same D:N ratio but whose protein metabolism was higher (13 per cent. of the total energy) the R. Q. was 0.691.

Magnus-Levy<sup>7</sup> has called attention to a possible reduction in the respiratory quotient when beta-oxybutyric acid is formed from fat. He estimates that the maximal quantity of beta-oxybutyric acid derivable from 100 gm. of fat is 36 gm. Under these circumstances, the respiratory quotient for fat would be reduced from 0.707 to 0.669. The case is not so simple, however, for if the 36 gm. of acid formed neutralized sodium bicarbonate, 15.23 gm. of carbon dioxide would be eliminated.

These relations are shown in Table 7:

TABLE 7.—THEORETICAL RESPIRATORY QUOTIENT WITH BETA-OXYBUTYRIC ACID FORMED FROM FAT

	Oxygen Liters	Carbon Dioxid Liters	R. Q.
100 gm. fat .....	201.9	142.73	0.707
36 gm. beta-oxybutyric acid .....	34.85	30.96	0.889
	167.05	111.77	0.669
Add for 15.23 gm. CO <sub>2</sub> from NaHCO <sub>3</sub> .....		7.74	
Possible end result .....	167.05	119.51	0.715

Since other bases than sodium bicarbonate may be used for the neutralization of beta-oxybutyric acid, it is apparent that the exact determination of the theoretical respiratory quotient when this acid is produced in large amounts in human diabetes is at present impossible.

This discussion has been prepared in order to further the understanding of a forthcoming description of metabolism in diabetes mellitus.

7. Magnus-Levy: Ztschr. f. klin. Med., 1905, lvi, 83.

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## VARIATIONS IN THE TOXICITY OF CHLOROFORM FOR ANESTHESIA \*

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In considering the toxicity of chloroform it is necessary to recall that a number of chemical processes are involved in its manufacture and that, in the various processes, a considerable number of chemical substances interact to give chloroform as one of the main products. Other products are formed, however, or remain from the mother substances which are used in the manufacturing process. The chloroform itself, of course, does not differ whether it be derived from acetone,<sup>1</sup> alcohol, methane, carbon tetrachlorid<sup>1</sup> or chloral, but there exist on the market many grades of chloroform, more or less contaminated with by-products of manufacture, in addition to the very best anesthetic grades freed from these products by purification, all of which are known under the general term "chloroform." Even chloroform of the anesthetic grade, however, is not pure  $\text{CHCl}_3$ , but contains in addition a small amount of alcohol (0.6 to 1 per cent. of 95 per cent alcohol).

It is evident from the foregoing that chloroform, which in itself could not have a variable toxicity, might, nevertheless, show such variability in even the anesthetic grades, owing to the possible presence of impurities derived either from the process of manufacture and subsequent incomplete purification or from decomposition products in a properly purified chloroform. In this connection is to be noted that pure  $\text{CHCl}_3$  undergoes decomposition more rapidly than  $\text{CHCl}_3$  to which a small amount of alcohol has been added, as occurs in the anesthetic grades. This introduces other factors, for, while proceeding more slowly, decomposition, especially in the presence of sunlight and air, occurs between the  $\text{CHCl}_3$ , alcohol and trace of water present in the alcohol.

Baskerville and Hamor<sup>2</sup> have made a careful study of the impurities to be found in chloroform and have divided them into two classes to

\* Submitted for publication Jan. 19, 1915.

<sup>1</sup> This investigation was undertaken at the suggestion of the Therapeutic Research Committee of the American Medical Association.

1. The most important sources of chloroform.

2. Baskerville and Hamor: Jour. Indust. and Engin. Chem., 1912, iv, 212.

indicate whether they come from the process of manufacture and improper purification or from oxidation products of pure chloroform and alcohol. Their study gives the following list of possible impurities:

A.—Excess water; excess alcohol; acetone; methyl alcohol; carbon tetrachlorid; tetrachlorethylene, hexachlorethane; aldehyds, chloral; higher alcohols and compounds; ether; acids (sulphuric, hydrochloric, formic, acetic), metallic chlorids; ethyl chlorid; ethylene chlorid; ethylidene chlorid; ethyl acetate; oils ("empyreumatic," "pyrogenous," "chlorinated"); fixed and extractive matter.

B.—Acetaldehyd; acetic and formic acids; carbonyl chlorid (phosgene); hydrochloric acid; hydrogen dioxid; chlorin; chlorin derivatives of alcohol oxidation products.

This array of possible impurities appears very formidable, although it may be stated at the outset that chloroform of anesthetic grade rarely, if ever, contains any of the impurities listed under A. Nevertheless, commercial chloroform containing some, at least, of these impurities has been used for anesthesia, so that they are of some importance. Chemical tests have been devised for their detection, however, and all chloroform intended for anesthetic purposes is subjected to such tests before being labeled "For Anesthesia."

Of more importance are the decomposition products which arise in properly purified chloroform when improperly stored. These changes arise subsequent to the time when chemical tests may be easily applied to detect their presence, since the anesthetist cannot very well make them. If they increase the toxicity of the chloroform definitely it would materially alter the present rather lax interest in the quality of the chloroform used in anesthesia.

While it is undoubtedly very desirable to use a chloroform free from all impurities and decomposition products, it has never been shown with any great degree of certainty that these substances are harmful, or at least, when present in mere traces, more harmful than pure chloroform. Such a demonstration is fraught with great difficulties, as is the estimation of the toxicity of any substance present in very small amounts in another substance, as chloroform, which in itself is markedly toxic.

Fiegel and Meier,<sup>3</sup> however, concluded that narcotic doses of pure chloroform had little or no action on the heart or general circulatory system and that depression of these organs arose from the impurities in chloroform. This, however, is not the current view. Schafer and Scharlieb<sup>4</sup> have pointed out the specific nature of the action of chloro-

3. Fiegel and Meier: *Biochem. Ztschr.*, 1906, i, 316.

4. Schafer and Scharlieb: *Jour. Physiol. Proc.*, 1903, xxix, 17.



form on the heart muscle, and Embley and Martin<sup>5</sup> have shown that such quantities in the blood as result from the administration of from 1 to 3 per cent. of chloroform vapor in air can paralyze the neuromuscular mechanism of the blood-vessels.

Of more direct bearing on the subject are the experiments of Waller,<sup>6</sup> who found that purified chloroform was more toxic than the concentrated impurities in chloroform. Likewise, Tunnicliffe,<sup>7</sup> after subjecting a good grade of chloroform to mechanical shaking and after exposing it to the direct action of sunlight, conditions under which chloroform is known to be rapidly oxidized, found that this chloroform did not differ at all from pure chloroform in its action on the heart.

Other reports such as these might be given, but the foregoing are sufficient to show that whatever the toxicity of the impurities in chloroform it cannot be very much in excess of that of chloroform, for otherwise there would not be such diametrical views.

This belief is supported also by a review of the toxic properties of the various impurities of commercial and anesthetic grades of chloroform. If one reviews the literature as to the toxic properties of the impurities given in Lists A and B, it will be found that the majority are far less toxic than a similar amount of chloroform. A considerable number, even, have been used as general anesthetics without disastrous results, although some were used in a considerably greater concentration than is considered safe with chloroform. Some are irritants only, although it is doubtful if they could possibly produce perceptible irritation if present only as mere traces. Apparently the two most toxic impurities of this sort are those which arise as decomposition products of pure chloroform, carbonyl chlorid and chlorin. It seems doubtful whether either of these could increase the harmful effects of chloroform materially, especially when considering that their dilution would be very great in anesthetic chloroform vapor.

Lehmann<sup>8</sup> has shown, however, that 1 part chlorin gas in 100,000 parts of air, if inhaled for some time, can cause bronchial irritation and hemorrhage and inflammation of the lungs. Likewise carbonyl chlorid, while probably not so toxic as chlorin, nevertheless has marked toxic properties, and both produce irritation of the tissues with which they come in contact. Both are said<sup>9</sup> to affect the anesthetist and those

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5. Embley and Martin: *Jour. Physiol.*, 1905, xxxii, 147.

6. Waller: *Nature*, 1907, lxxvi, 402.

7. Tunnicliffe: *Pharm. Jour.*, xviii, 315.

8. Lehmann: *Arch. f. Hyg.*, 1903, xlvi, 322.

9. Lee: *Liverpool Med. Chir. Jour.*, 1895, xv, 412. Buxton: *Brit. Med. Jour.*, 1912, i, 582.

above the patient rather than the patient himself, indicating gases lighter than air.

In view of these considerations, it seems particularly doubtful whether animal experiments would add any information indicating differences in the toxic properties of chloroform; at least, in that of anesthetic grade. Nevertheless, some experiments were undertaken, for which purpose four samples of anesthetic chloroform of different brands<sup>10</sup> were secured in original containers which, together with a sample of anesthetic chloroform which had been standing in the laboratory exposed to the light for at least two years in a half filled white glass bottle, comprised the series studied in this report. In the discussion of these samples they are to be identified by the numbers from 1 to 5, of which No. 5 designates the laboratory sample of chloroform.

In the first series of experiments white mice of the same lot (approximately of the same age and weight and fed on the same kind of food) were used to determine differences in the toxicity of Chloroforms 1, 2 and 3. The method was the following:

Two-liter flasks were fitted with tightly fitting stoppers through which was passed a thermometer. A mouse was placed in each of several flasks and a carefully measured amount of the chloroform in question was pipetted directly on a piece of gauze suspended inside the flask. The flask was immediately tightly stoppered and the time noted. Observations were then continuously made until the animal died, and a record was made of the symptoms observed and the time of death. The time consumed before the chloroform produced death was taken as a measure of its toxicity. Before the flasks were used again for further experiments the chloroform vapor was blown out, using compressed air. The results of these experiments are to be found in Tables 1 to 5.

It is evident from the figures in Tables 1 to 6 that wide variations occur not only in the figures of a single series, but also in the averages of the different series. Particularly is this true of the averages in Series 1, 2 and 3, but Series 4 and 5 show similar variations, although the averages are very similar. The discrepancies in the general averages of Series 1 to 3 largely disappear, however, when these are averaged, so that the difference is less marked. Accepting these final figures as only possibly correct, one has the relation of toxicity as follows:

A. Chloroform 1.....	16.0
Chloroform 2.....	17.5
B. Chloroform 1.....	26.62
Chloroform 3.....	26.92

10. Squibb & Sons, Parke, Davis & Co., Mallinckrodt Chemical Works, and Albany Chemical Company.

TABLE 1.—SERIES 1. DOSE 0.15 C.C. PER 2,000 C.C. FLASK

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 2	Chlor.	Minutes
25	22.5	13			
26	24.0	..	37	1	18
27	24	..	22		
28	23.5	18			
29	23	19			
30	23	..	41		
31	23	..	33	2	33.25
32	23	23			
33	23.5	17			

TABLE 2.—SERIES 2. DOSE 0.2 C.C. PER 2,000 C.C. FLASK

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 2	Chlor.	Minutes
19	22.5	16			
20	22	8			
21	24	6	..	1	10
22	23.5	..	8		
23	23.5	..	8		
24	23	..	10	2	8.66

TABLE 3.—SERIES 3. DOSE 0.2 C.C. PER 2,000 C.C. FLASK

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 2	Chlor.	Minutes
62	23.5	17			
63	23.5	34		1	20
64	23.5	36			
65	23	6			
69	22	35			
71	23.5	12			
66	23.5		11		
67	23		11	2	10.75
68	24		8		
70	23.5		13		

TABLE 4.—SERIES 4. DOSE 0.18 C.C. PER 2,000 C.C. FLASK

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 3	Chlor.	Minutes
38	23	35		1	28.5
41	23	27			
44	24	37			
47	23	29	..		
50	23.5	10			
51	23.5	33		3	28.1
36	23	..	44		
37	23	..	14		
40	23	..	34		
42	23	..	11		
43	24	..	14		
45	23	..	16		
46	23	..	10		
48	23	..	47		
49	23.5	..	17		
52	23	..	47		
53	23	..	55		

TABLE 5.—SERIES 5. DOSE 0.2 C.C. PER 2,000 C.C. FLASK

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 3	Chlor.	Minutes
54	23	30		1	24.75
56	22	22			
57	22	12	..		
61	23	35	..		
55	22	..	13		
58	23	..	30	3	25.75
59	22.5	..	35		
60	23	..	25		

TABLE 6.—SUMMARY OF AVERAGE TIME TILL DEATH, SERIES 1 TO 5

	Chloroform		
	1	2	3
Series 1....	18.00	33.25	
Series 2....	10.00	8.66	
Series 3....	20.00	10.75	
Series 4....	28.5	.....	28.1
Series 5....	24.75	.....	25.75

Reducing these figures to a percentage basis and assuming that the most toxic of these samples when measured by the rapidity of death is 100 per cent., one obtains the following figures:

Chloroform 1 .....	100.0
Chloroform 2 .....	91.4
Chloroform 3 .....	98.8

The difference in toxicity shown here of 8.6 and 1.2 per cent. cannot be accepted as absolute differences since these figures were derived from general averages, the individual figures of which varied so widely. They seem more than merely the result of chance, however, and it seemed advisable to continue these experiments along somewhat different lines, using a much larger number of animals, so that the law of averages would more surely hold good.

TABLE 7.—AVERAGE TIME TILL DEATH OF FISH

Sample	1	2	3	4	5
Series 3....	66	77	85	48	69
Series 4....	94	149	143	85	97
Series 5....	97	119	152	166	142
Series 6....	148	77	94	141	110
Series 7....	85	122	123	115	92
Series 8....	158	141	197	206	178
Series 9....	157	170	155	99	148
General average	115.0	122.1	137.0	122.8	119.3

TABLE 8.—PERCENTAGE OF DEATH IN FISH EXPERIMENT

Sample	1	2	3	4	5
Series 3....	100	80	90	80	70
Series 4....	60	60	60	60	70
Series 5....	30	70	80	80	80
Series 6....	100	80	80	90	90
Series 7....	70	90	90	80	60
Series 8....	80	70	80	70	60
Series 9....	60	40	70	80	90
Average ...	71.4	70.0	78.6	77.1	74.3

A further series of toxicity experiments was devised, small trout being used instead of white mice. In these experiments a measured amount of the chloroform to be tested was dissolved in water of a constant temperature, the chloroform being dissolved by agitation with the water in a glass-stoppered measuring flask of appropriate size.

A suitably diluted chloroform water after having been prepared in this way, was poured into large glass jars and a lot of ten fish added by lifting them from the storage tank in a dip net. In all cases, all the chloroforms under examination were tested at the same time by allowing an interval of thirty seconds to intervene between each transfer of a given lot of fish to the chloroform water. At varying periods of from twelve to forty minutes thereafter the fish were again transferred with the dip net from the chloroform water to fresh tap water and the time was noted when the fish stopped breathing, as indicated by the cessation of gill movements. This was taken as one of the indications of toxicity. The other indication was the survival or death of the fish of each lot. At first, dilutions of 1 part chloroform to 2,500 parts water were tried, but this was found to be too toxic, and later, dilutions of 1 part to 8,000 to 10,000 parts water were found to prolong the intoxication sufficiently for accurate observation. The results of seven series of such experiments with Samples 1 to 5, involving 350 fish, are to be found in Tables 7 and 8, in which are given the average time till death of such fish as were killed and also the total number of dead in each lot. Temperatures and the length of time the fish were in the chloroform water are not given, but were always constant with the five samples of chloroform for an entire series.

It will be seen from these tables that here, as in the earlier experiments on mice, wide variations are to be found in the figures of individual experiments. Eliminating the results of time till death,<sup>11</sup> however, it is noticeable that the differences in the toxicity of the various samples of chloroform are not marked, especially when considering the wide variations in individual experiments in which the order of toxicity is different for every series. It must be concluded on this account, then, that this method does not lend itself to a determination of the extremely slight differences, if any, in the toxicity of anesthetic grades of chloroform. This is especially emphasized by the result with Chloroform 5, the laboratory sample of chloroform 2 years old, which occupied an intermediate place in its toxicity, although it would be presumed that this sample would possibly be the most toxic of the five samples.

A final series of experiments on trout was carried out to determine whether the toxicity of chloroform could be accentuated by fractional distillation. Samples 1 and 5 were chosen for these tests. Each was distilled so that three fractions were obtained as follows: below 60 degrees, Samples 1<sub>1</sub> and 4<sub>c</sub>; between 60 and 61 degrees, Samples 2<sub>1</sub> and

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11. It seems advisable to eliminate these figures in estimating the toxicity of a given chloroform as this is not nearly so important as the fact of death itself in measuring toxicity. These figures have been introduced into this and a later table merely to show the lack of relationship between them.



5<sub>2</sub>; above 61 degrees, Samples 3<sub>1</sub> and 6<sub>5</sub>. The middle fraction, between 60 and 61 degrees, was in both cases the largest part of the distillate. The manner of making the dilutions and of experimentation were the same as in the preceding series. The results are to be found in Tables 9 and 10.

TABLE 9.—AVERAGE TIME TILL DEATH IN FINAL EXPERIMENTS ON TROUT

Sample	1 <sub>1</sub>	2 <sub>1</sub>	3 <sub>1</sub>	4 <sub>5</sub>	5 <sub>5</sub>	6 <sub>5</sub>
Series 1....	132	139	163	...	...	119
Series 2....	123	...	98	117	125	88
Series 3....	59	65	84	76	79	...
Series 4....	...	90	...	98	97	77
Average ...	104.6	98.0	115.0	97.0	100.3	94.6

TABLE 10.—PERCENTAGE OF DEATH IN TROUT

Sample	1 <sub>1</sub>	2 <sub>1</sub>	3 <sub>1</sub>	4 <sub>5</sub>	5 <sub>5</sub>	6 <sub>5</sub>
Series 1....	70	70	60	...	...	70
Series 2....	70	...	90	90	100	90
Series 3....	90	80	80	80	80	...
Series 4....	...	70	...	70	80	90
Average ...	76.6	73.3	76.6	80.0	86.6	83.3

TABLE 11.—PERCENTAGE OF TOXICITY OF CHLOROFORM

	Chloroform				
	1	2	3	4	5
Mice .....	100.0	91.4	98.8	...	...
Trout .....	100.0	98.0	110.1	107.9	104.0
Trout distillates....	100.0	...	...	...	110.3

In this series of experiments also, there is no relation between the time till death and the percentage of deaths even in the general averages. Taking the percentage of death as a criterion of toxicity, however, it appears that Distillate 2<sub>1</sub>, 60 to 61 degrees is the least toxic among the distillates from Sample 1, whereas the similar Distillate 5<sub>5</sub>, 60 to 61 degrees, is the most toxic of the distillates from Sample 5, 13.3 per cent. more deaths resulting from the latter.

Another fact developed is that the average toxicity for the distillates from Sample 1 is 75.5 per cent.; for those from Sample 5 it is 83.3 per cent., a difference of 7.8 per cent. This becomes particularly interesting when it is noted that the difference between the original chloroforms before distillation was only 2.9 per cent. This indicates an error of 4.9 in the percentage of deaths and shows that, in spite of the wide variations in single experiments, the method gives reasonably accurate results. It also shows, inasmuch as the differences in the percentage of deaths between the various samples of chloroform were found not to exceed 8.6 per cent., that there cannot be said to be any certainly demonstrable difference in the toxicity of these samples, for errors in results would easily account for the differences found.

A comparison of the toxicity of the five samples of chloroform as obtained in the three different methods of experimentation, on the basis that the toxicity of Chloroform 1 equals 100 per cent., is given in Table 11.

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# THE RELATION OF THE PURGATIVE ACTION OF MAGNESIUM SULPHATE TO PERISTALSIS, AND THE GENERAL LAW OF CROSSED INNERVATION \*

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While the subject I intend to discuss in particular is the inhibitory rôle of magnesium salts in its relation to the production of intestinal peristalsis, my chief object is to set forth certain general views I hold now, and have held for many years, on the subject of inhibition in general and the rôle which it plays in the mechanism of all sorts of movements in the animal organism. I shall begin the discussion of the relation of magnesium salts to peristalsis by calling attention to two sets of facts which seem to contradict each other.

It is a well-known and well-established fact that magnesium sulphate, or Epsom salts, is one of the most efficient purgatives. There have been many discussions as to the cause of the action of saline purgatives. According to one view, which has undergone many variations in its details, the cause of the purgation consists in the power of the saline to bring about an accumulation of liquid within the lumen of the intestine. We need not discuss here the nature and origin of this liquid. For our purpose it suffices to say that no matter from what cause liquid accumulates within the intestine, its mere presence would not cause purgation without the mediation of peristaltic movements of the intestinal canal. It is a known fact that the presence of large quantities of liquid within a paralyzed intestine does not lead to evacuation. According to another view which in recent years has been brought forward again by pupils of Jacques Loeb, the cause of action of certain purgative salts consists directly in their ability to stimulate the neuromuscular apparatus of the peristaltic mechanism. According to all views, then, peristaltic movements are indispensable for purgation, and therefore magnesium sulphate as an efficient purgative is expected to increase, or at least not to inhibit, the peristaltic movements of the intestines. I hardly need add that under the term peristalsis is generally meant a progressive movement of a vermiform character, which

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in our special case, means a vermiform movement of the gastro-intestinal canal running in an aboral direction.

Now in apparent opposition to the mentioned fact, I have to enumerate a number of observations which were safely established in our laboratory in the course of the last few years. In experiments carried out by Auer and myself several years ago, in which the behavior of the intestines of rabbits was observed in a warm bath of normal saline, we found that intravenous injections of magnesium salts stop peristaltic movements promptly. Usually not much peristaltic movement of the intestines can be seen, when the abdomen of a rabbit is opened. In order to observe the effect of magnesium sulphate, peristaltic movements had to be brought on by artificial means: by intravenous injections of sodium sulphate, barium chlorid, physostigmin or ergot, or by the destruction of the spinal cord. The peristaltic movements brought on by these means were sometimes of a violent character. All these peristaltic movements were either completely inhibited, or at least greatly reduced, by an intravenous injection of a solution of magnesium sulphate (or magnesium chlorid). In a later series of experiments, carried out by Don R. Joseph and myself, a method was employed in which the peristaltic movements could be studied in animals whose abdomens were closed. At one sitting the abdomen of rabbits was opened under proper anesthesia, and catheters, bearing at one end a small balloon, were inserted into the lower part of the duodenum and into the stomach; stomach, duodenum and abdomen were then properly closed. In the following days the protruding end of each catheter was connected with a graphic apparatus and tracings representing the peristaltic movements of the stomach and the duodenum were obtained. There were in nearly all cases good, spontaneous movements of the stomach and the duodenum. We have, then, established beyond a doubt that the action of magnesium sulphate on the stomach and the duodenum is, under all circumstances, only of an inhibitory character. Whether the peristaltic movements were spontaneous in origin, or were brought about or intensified by barium chlorid or other substances, an intravenous injection of magnesium sulphate, even in an isotonic concentration, invariably caused an immediate inhibition, or at least an unmistakable reduction, of the persistalsis, lasting for some time after the injection has ceased.

These experimental results were obtained, as I stated before, by intravenous injections of the magnesium salts. I am now in a position to state, however, that the same inhibitory results can be readily obtained when the magnesium solutions are introduced into the lumen of the intestine. Auer and I found that magnesium salts, when introduced into the lumen of the intestine, are readily absorbed and may

cause respiratory paralysis and death of the animals within a short time after the injection. Recently I have studied the effect of such a direct introduction of magnesium salts into the lumen of the intestine on the behavior of the peristaltic movements of the latter. I found that the intestine becomes practically paralyzed. I shall mention here one striking result. When the trachea of an animal is clamped and the animal thus killed by asphyxia, the exposed intestines show more or less strong peristaltic movements. When, however, a solution of magnesium salts is previously introduced into the lumen of the intestine, no part of the gastro-intestinal canal shows movements worth mentioning during or after the asphyxia.

These various experimental observations show unmistakably that magnesium salts, whether given intravenously or introduced into the lumen of the intestine, not only do not cause any peristalsis of the intestine, but positively inhibit it, when it is present. The puzzling question which now presents itself is this: If magnesium sulphate causes a suppression, an inhibition of the peristaltic movements, and only an inhibition, how can it bring on purgation in which, as we have seen above, peristaltic movement of the intestine is an indispensable factor?

To answer this question I shall have to enter into an analysis of inhibition and the rôle it plays in peristalsis. All know what is meant by inhibition. The best known type of it is the phenomenon with which all are acquainted; it is the fact that the stimulation of the end of the vagus which goes to the heart stops the beating of that organ. The heart is a muscle. A nerve going to a muscle we usually term a motor nerve. Stimulation of such a nerve causes contraction of the muscle pertaining to it. But stimulation of the end of the vagus which goes to the heart stops the heart from beating. That is inhibition. Numerous other examples and other forms of inhibition are now well known. One of them is, that stimulation of the end of the splanchnic nerve which goes to the intestines, stops peristalsis of the intestine; it inhibits the peristalsis. Here we have some evidence that the phenomenon of inhibition may be connected with the peristalsis of the intestines. However, the most striking fact that inhibition is actually concerned in the peristaltic movements of the digestive tract was made by us thirty-four years ago in our studies of the function of deglutition. We then first established that after each beginning of a deglutition various parts of the esophagus develop a peristalsis at various intervals, according to their distances from the tongue and pharynx. For instance, the peristalsis of the cervical part of the esophagus sets in about two seconds after the beginning of deglutition; the esophagus in the upper part of the thorax begins to contract about three seconds, the part of the esophagus above the diaphragm begins to contract about six

seconds, after the deglutition. These data were obtained from observations on my own esophagus. We discovered in the course of these studies that, when the deglutitions are repeated, say in less than every three seconds, the upper part of the thoracic esophagus does not contract after each deglutition, but only after the last deglutition has taken place. The same applies for the cervical as well as the lower part of the esophagus. In other words, with each deglutition which sends down an impulse for a contraction of the peristalsis, also an inhibitory impulse is sent down along the esophagus—for the purpose of inhibiting any possible contraction which may be present in any part of the esophagus, due to a previous act of deglutition. I may say here that each deglutition inhibits also the presence of a tonus in the esophagus. This physiological phenomenon reminds one of the precautions which are taken when an express train is sent off; along the entire road telegraphic messages are sent, to keep the tracks free. That is the sense of the inhibitory wave which runs ahead of the peristaltic contraction to keep the track free.

Some thirty years ago I tried to generalize this point of view, to apply it to all functions of the body which require definite movements. I stated then, that, for instance, for the extension of the leg it is necessary that the flexors should be inhibited from being contracted simultaneously, or from remaining in a state of tonus. At that time I illustrated the actual occurrence of such antagonistic relations by the behavior of the function of respiration; during each inspiration the contraction of the expiratory muscles is inhibited, and during each expiration the diaphragm and other inspiratory muscles are suppressed, inhibited.

I wish to dwell a little longer on that subject. You probably know that these relations of flexors and extensors, as I anticipated them many years ago, have been brilliantly studied since 1895 by Sherrington, who terms the relations of flexors and extensors "reciprocal innervation." That designation is for these specific relations proper enough, because just as the flexors become inhibited, when the extensors have to contract, the extensors also become inhibited when the flexors are contracting. It is, then, a truly *reciprocal* innervation process. But when we apply these relations to a canal in which movements go on only in one direction, there is, of course, only one-half of this process. It is always only the lower part of the canal which has to be relaxed, when the upper part is contracting. A true antiperistalsis does not exist. In order to comprise all these phenomena under one head, I term the relations under discussion as "contrary innervation." It produces simultaneously a contraction in one part and an inhibition in another—in the contrary part. That means, two parts which are



concerned in a single function are simultaneously innervated in a contrary way. The upper part of the canal is contracting in order to move the contents downward and the lower part is relaxing in order to remove any obstacle to this motion.

We shall now turn back to the digestive tract. I shall mention here first that, on the basis of these considerations, we discovered long ago that with each act of deglutition the tonus of the cardia becomes inhibited—to open the gate into the stomach for the entrance of the contents which are swallowed down. In recent years Joseph and I found that during each contraction of the pyloric part of the stomach an inhibition of the movements of the duodenum takes place. Cannon and Lieb found that during a peristaltic contraction of the esophagus a simultaneous relaxation of the stomach makes its appearance. Finally, Lyman has observed that the colon becomes motionless and relaxed while the material is driven through the ileocolic sphincter by peristalsis in the ileum. All these observations have evidently that one background in common, namely, that for the purpose of moving downward the contents of the gastro-intestinal canal, the distal part of the various sections of the canal become inhibited, while the adjoining proximal (upper) part of the corresponding section gets into a state of contraction—a manifestation of the Law of Contrary Innervation.

Of greater interest to our problem is the instructive observation which was made by Bayliss and Starling some seventeen years ago, namely, that a stimulation of the intestines at any place causes a contraction above the point of stimulation and a relaxation or inhibition of the part of the intestine below the point of stimulation. Bayliss and Starling called this phenomenon the Law of the Intestines. But it is evident that this phenomenon is the law not only of the intestines, but of the entire digestive canal and that it is, furthermore, a part of the phenomenon which I term "Contrary Innervation."

The outcome of the foregoing facts under consideration, bearing on the intestinal peristalsis, is evidently this: A peristaltic movement does not consist merely in a vermiform downward moving contraction; peristalsis is made up of two simultaneous phenomena: a contraction of the upper part and a relaxation or an inhibition of the lower part of the section of the gastro-intestinal canal, engaged in the act of moving downward some of its contents.

Bayliss and Starling have shown that this dual response of the intestine to a single stimulus takes place even when the intestines are freed from their extrinsic innervation. They thought that the process is of a myogenic origin; but Magnus has shown conclusively that it is connected with Auerbach's plexus, the myenteric plexus, located between the longitudinal and circular sheaths of the fibers of the intes-

tinal muscularis. We may, therefore, formulate our conclusion in the following terms: A stimulation of the myenteric plexus produces simultaneously a double effect, a contraction of the muscle fibers above, and an inhibition of any contractions below the point of stimulation.

I shall now turn my attention to the relation of magnesium sulphate to the phenomenon of inhibition. About sixteen years ago, when studying the effect of intracerebral injection of various salts, I came across the following surprising fact: While the injection into the cerebrum of many other salts produced characteristic convulsions, the injection of a few drops of a 5 per cent. solution of magnesium sulphate caused the rabbit to turn over on one side and remain lying in a state of stupor and relaxation. With a long standing interest in the phenomenon of inhibition it was quite natural for me to interpret the stuporous and relaxed condition of the animal as possibly being a state of inhibition. In the many studies of the action of salts on the animal organism to be found in the physiological and pharmacological literature, the effects observed and studied were always those of the exciting action of the salts. It was from the point of view that possibly the magnesium ion in the body is chiefly concerned in the inhibitory processes, that we started our various studies on the effects of magnesium. It became a working hypothesis; we had not yet come across some definite, weighty facts which are capable of disproving this hypothesis. As to the relations of magnesium salts to the gastrointestinal canal, it has been stated before, that in the studies of Auer, Joseph and myself no other effect was found but that of inhibition of the peristaltic movements of the intestine.

We come now to our original question; it is this: On the one hand, it is certain that magnesium salts cause purgation, a process in which peristalsis must be a factor; on the other hand, the extensive experimental studies revealed the unmistakable fact that magnesium salts inhibit intestinal peristalsis. How can we reconcile these apparently contradictory facts? My answer to this question, given merely in a general way, is this: 1. The phenomenon of peristalsis does not consist alone in a contraction of a certain part, but in a contraction of the proximal and *relaxation of the distal part* of a section of the intestine. 2. The effect of magnesium sulphate on peristalsis may consist chiefly in its relation to the inhibitory part of the phenomenon of peristalsis.

As I have just indicated, my answer to the central question shall be of a general character; I am unwilling for the present, to enter on definite statements as to how magnesium affects the peristalsis. I am confident that details which I may venture to state now will have to be modified by facts which future experimental investigations are sure to bring to light. I shall, however, try to continue the analysis by dis-

curring briefly a few points which may have some bearing on the subject.

1. We have seen above that a stimulation of any part of the intestine causes by means of the intrinsic myenteric plexus (and probably also by the aid of the extrinsic innervation), a contraction above and a relaxation below. How strong the contraction of the part above may be and how intense is the inhibition of the part below, and how far it may extend, depends on a variety of circumstances. In the first place, we must here, as everywhere, distinguish between *irritability* and *stimulation*. Increase of irritability alone can bring out no action without the incident of a stimulus. The irritability of the concerned innervation may be low or high and may concern the exciting and inhibitory phases in various degrees. For instance, magnesium salts may increase exclusively or essentially the irritability of the inhibitory phase, while other salts, for instance, sodium sulphate, may increase preferably or exclusively, the irritability of the exciting phase. There is good reason for the assumption that the increase of irritability occurs through the circulation; but we have no definite evidence that this may not occur also by mere action on the periphery.

Again, stimulation may affect preferably the exciting phase or the inhibitory. But we are rather inclined generally to assume that a stimulus affects, as a rule, both the exciting and the inhibitory phases simultaneously. We are also inclined to assume that the point of attack of a stimulus is to be found at the periphery. But there is no evidence against the assumption that stimulation may take place also directly through the circulation. We need hardly add that a stimulus may be weak or may be strong.

Taking all these points together, it can be seen at a glance how variable the effects of some substances on the intestine may be. With a low irritability of certain sections of the intestine, and with a comparatively low stimulus from the periphery, the effect may be altogether circumscribed, and the result may be, not peristalsis, but only "segmentation," the effect of each stimulus not being an intense contraction above and not an extensive relaxation below. With an increased irritability and with a moderately strong stimulus, there may be a fair contraction above and a fairly extensive relaxation below, and the result will be a peristalsis extending over a fairly large section. With a strongly increased irritability of both phases and with a strong stimulus, the result may be a rapid peristalsis, running through the entire intestine within a very short time, a condition which we termed "peristaltic rush."

2. A brief discussion of peristaltic rush will not be amiss here. As was just stated, by "peristaltic rush" we designate the phenomenon of a rapid peristaltic movement running downward through the entire small intestine within a fraction of a minute. This phenomenon was observed for the first time by Van Bram-Houckgeest some forty years ago in rabbits dying from asphyxia. He termed it *Rollbewegungen*. Several years ago Auer and I succeeded in producing this phenomenon practically at will in living rabbits. The method we used consisted in injecting intravenously antagonistic substances; that is, one substance which favors contractions of the gut, and another which favors the inhibition of such contractions; for instance, ergot and magnesium sulphate.

3. Our experimental studies of the inhibitory effect of magnesium salts on peristalsis were made either by administering magnesium sulphate intravenously or by injecting it into the lumen of the small intestine. However, when administering magnesium sulphate by mouth (as for the purpose of purgation), while the salt passes through the stomach it meets with sodium chlorid and some carbonates. It is therefore possible, and even probable, that parts of the magnesium sulphate become converted into sodium sulphate and magnesium carbonate. Sodium sulphate is soluble and is readily absorbed. From the experiments of MacCallum and of Auer we know that sodium sulphate when given intravenously is apt to bring on some peristalsis. Magnesium carbonate is not soluble and remains within the intestine probably entirely unabsorbed. We know that magnesium carbonate is capable of acting as a purgative. The insoluble carbonate acts possibly within the intestine in two ways: on the one hand, it attracts liquid into the lumen of the intestine thus distending it, and, on the other hand, the carbonate is likely to serve as a chemical stimulus directly on the mucosa. At any rate, it is not impossible that that part of the magnesium sulphate which has been converted into a carbonate acts within the intestine as a stimulus calling forth peristaltic movements. On the other hand, the part of the magnesium sulphate which is converted into sodium sulphate may be the means of increasing the irritability of the exciting phase of the peristalsis; it may serve also as a stimulus to the neuromuscular apparatus. The remaining unconverted portion of the magnesium sulphate increases the irritability of the inhibitory phase of peristalsis. Now we have seen above that by the administration of antagonistic substances, that is, substances, one of which increases the exciting phase, while the other increases the inhibitory phase of peristalsis, are capable of calling forth a "peristaltic rush," that is, a peristaltic wave which runs rapidly through the entire small intestine within a short time. We can therefore easily conceive that the

purgative action of magnesium sulphate, when administered by the mouth, results from the fact that a part of it acts by increasing the inhibitory phase of peristalsis, while other parts, by being converted partly in sodium sulphate and partly into magnesium carbonate, increase the irritability of the exciting phase of peristalsis and serve as an inciting stimulus to start peristaltic movements. The result is the development, after some time, of partial and perhaps complete peristaltic rushes.

I wish to repeat again that I offer this detailed analysis of the action of magnesium sulphate merely as a preliminary hypothesis. Future experimental work will throw more light on these questions.

4. In a few words, my general conception of the various effects which may result from the simultaneous actions of exciting and inhibitory factors on the functions of the animal body are as follows: The resultant effects of the antagonistic actions can be of a threefold nature which may be designated as *tonus*, *rhythm* and *peristalsis*.

1. The resultant effect of the antagonistic actions may be *manifest at the same place and at the same time*. This is a *tonus*. The degree and the character of the tonus depend on the preponderance of one or the other factor.

2. The effect of both antagonistic factors may be *manifest at the same place, but at different, alternating times*. It is then a *rhythm*; contraction alternates with inhibition.

3. Both effects of the antagonistic factors may be present *at the same time, but manifest themselves simultaneously in different parts*. The resultant is then, as far as the intestines and other muscular tubes are concerned, a *peristalsis*; a contraction above and an inhibition below.

STUDIES IN RENAL FUNCTION WITH SPECIAL REFERENCE TO NON-PROTEIN NITROGEN AND SUGAR CONCENTRATION IN THE BLOOD, PHENOLSULPHONEPHTHALEIN ELIMINATION AND BLOOD PRESSURE \*

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Until the theories of nephritis are reduced to one and until that one has been conclusively proved to be correct, continued investigations, both clinical and experimental, seem to be demanded.

These studies in nephritis deal on the one hand, with the accumulation or retention in the blood of the end-products of protein metabolism and glucose concentration in the blood, and on the other hand, with the functional capacity of the kidneys in so far as the latter may be determined by the elimination of phenolsulphonephthalein. In short, the purpose of this paper is to study:

1. The relation of protein feeding to nitrogen retention in the blood.
2. The relation of nitrogen retention to renal function.
3. The relation of blood-sugar, blood-pressure, phenolsulphonephthalein elimination and nitrogen retention.

So far as we can ascertain, there have been no studies covering all of these phases simultaneously and the possible relationship existing between them; though quite recently Folin<sup>1</sup> and Frothingham and Smillie<sup>2</sup> have reported on somewhat similar studies, the latter presentation having been published shortly before the completion of this work.

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1. Folin, Otto, Denis, W., and Seymour, Malcolm: The Non-Protein Nitrogen Content of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, *THE ARCHIVES INT. MED.*, 1914, xiii, 224.

2. Frothingham, Channing, and Smillie, Wilson, G.: The Relation Between the Phenolsulphonephthalein Excretion in the Urine and the Non-Protein Nitrogen of the Blood in Human Cases, *THE ARCHIVES INT. MED.*, 1914, xiv, 541.



## I. THE RELATION OF PROTEIN FEEDING TO NITROGEN RETENTION IN THE BLOOD

With but two exceptions, these observations were made on ward patients in the University Hospital on the service of Dr. Alfred Stengel.

To study the effect of the level of protein diets on the retention of nitrogen in the blood, we first placed the patient on a diet of about 2,300 calories, which represented approximately 5 gm. of nitrogen; then on a diet of 2,150 calories, corresponding to 12 gm. of nitrogen, and finally, on a diet of 2,300 calories or about 18 gm. of nitrogen.

TABLE 1.—INFLUENCE OF PROTEIN FEEDING ON RETENTION OF NITROGEN IN BLOOD IN CARDIORENAL DISEASE

Case	Diagnosis	Age	Sex*	Date	Nitrogen per hundred c.c. of blood, mg.		
					Low Protein Diet	Ward Diet	High Protein Diet
1. J. H. B.	Chronic nephritis; chronic endocarditis	39	♂	4/1	23	18	30.8
2. J. McW.	Chronic nephritis; chronic myocarditis	48	♂	4/1	28	28	35.5
3. J. H.	Chronic interstitial nephritis; chronic myocarditis	34	♂	4/1	....	28	33.6
4. J. W.	Chronic nephritis; chronic myocarditis	45	♂	4/2	26	28	
5. H. L.	Chronic interstitial nephritis; myocardial weakness; arteriosclerosis	55	♂	5/9	26	32	39
6. A. P.	Chronic nephritis; chronic myocarditis	49	♂	5/9	30	36	39
7. L. S.	Chronic interstitial nephritis; myocardial weakness	55	♀	7/21	23	30	37
8. S. C.	Arteriosclerosis.....	70	♀	7/21	18	26	35
9. F. G.	Chronic nephritis; chronic myocarditis; asthma	49	♀	10/19	29	28	

\* In this and the following tables, ♂ denotes male, and ♀ female.

The duration of each period was three days, and in the afternoon of the third day the blood was withdrawn from a vein in the arm and analyzed according to the recent method of Folin and Farmer<sup>3</sup> with the modification that the ammonia liberated was collected in standardized fiftieth normal sulphuric acid and titrated with fiftieth normal sodium hydroxid. It is generally conceded that by this method normal values are those with a total nitrogen of less than 30 mg. per hundred c.c. of blood. We found that all but two cases revealed higher figures at the end of the high protein diet, as will be seen in Tables 1 and 2.

3. Folin, O., and Farmer: Jour. Biol. Chem., 1912, xi, 527.

which are good illustrations of the influence of protein feeding on the retention of nitrogen in nephritics.

In several cases of pure nephritis of the chronic interstitial type and in which there was an increase in non-coagulable nitrogen on a low protein diet, there was a striking reduction in tolerance for an increasing amount of proteid, as was shown by the marked rise in retention products as well as by nausea and vomiting in a few cases (Table 2). Clinically, these results indicate not only the importance of a low proteid diet in certain types of nephritis, but they also illustrate the advantages of this test for a more accurate diagnosis of these types.

TABLE 2.—RISE IN RETENTION PRODUCTS FOLLOWING INCREASE IN PROTEIN INGESTION IN CASES OF CHRONIC INTERSTITIAL NEPHRITIS

Case	Diagnosis	Age	Sex*	Date	Nitrogen per hundred c.c. of blood, mg.		
					Low Protein Diet	Ward Diet	High Protein Diet
1. W. P.	Chronic interstitial nephritis	65	♂	4/1	26	33	40
2. L. L.	Chronic interstitial nephritis	55	♀	4/1	29	30	32
3. D.	Chronic interstitial nephritis	55	♀	4/9	43	54	60
4. G. C. B.	Chronic interstitial nephritis	40	♂	2/26	28	25	43
5. M. W.	Chronic interstitial nephritis	28	♀	5/4	43	35	
6. Mr. R.	Chronic interstitial nephritis	27	♂	6/15	67	88	92
7. S. R.	Chronic interstitial nephritis	26	♂	6/28	56		
8. E. B.	Chronic interstitial nephritis	43	♂	7/6	30	46	56
9. E. H.	Chronic interstitial nephritis	21	♀	7/7	22	29	37
10. P. F.	Chronic interstitial nephritis	61	♂	6/13	39	33	42
11. M. L.	Chronic interstitial nephritis	53	♀	10/1	36	37	
12. S. B. J.	Chronic interstitial nephritis	43	♂	11/27	50		

In fact, observations on nitrogen retention are becoming more and more frequent in the literature. Macwitz, Rosenberg and Tscherkoff,<sup>4</sup> in an exhaustive study of the pathology of nephritis and its functional diagnosis by various tests, conclude that nitrogen retention is indicative of vascular disease and that, in chronic cases, it is a good index of the degree of insufficiency and gives a valuable clue for both prognosis and therapy.

With regard to the influence of chronic passive congestion on nitrogen retention in the "cardiorenal" symptom-complex, our results

4. Macwitz, Rosenberg and Tscherkoff: München. Med. Wehnschr., 1914, No. 23, p. 1268.

TABLE 3.—RESULT OF EXAMINATION OF A SERIES OF CARDIORENAL CASES

Case	Diagnosis	Age	Sex	Blood Nitrogen Mg. per 100 c.c. of Blood	Blood Sugar Gm. per 100 c.c. of Blood	Phtha- lein Elimi- nation % in 2 Hrs.	Blood Pressure	Eye-Grounds	Edema Liver <sup>*</sup>	Albu- min	Casts	Sp. Gr.
1. J. H. R.	Chronic nephritis; chronic endocarditis	39	♂	23	0.07	10	110/69	.....	++	+	+	1.007
2. J. McW.	Chronic nephritis; chronic myocarditis	48	♂	28	0.076	46	135/98	.....	++	++	++	1.025
3. J. H.	Chronic interstitial nephritis; chronic myocarditis	34	♂	28	0.085	40	100/130	Early sclerosis	++	+	+	1.015
4. J. W.	Chronic nephritis; chronic myocarditis	45	♂	26	0.09	45	138/70	.....	++	++	++	1.021
5. H. L.	Chronic interstitial nephritis; myocardial weakness; arteriosclerosis	75	♂	26	0.131	30	155/90	Indentation of veins. Arteries thickened	—	+	+	1.015
6. A. P.	Chronic nephritis; chronic myocarditis	49	♂	30	0.159	15	150/90	.....	+	++	++	1.025
7. L. S.	Chronic interstitial nephritis; myocardial weakness	55	♀	23	.....	25	155/80	Moderate sclerosis	+	+	—	1.017
8. M. C.	Chronic interstitial nephritis; chronic myocarditis	41	♀	28	0.09	8	158/105	Incipient sclero- tic changes	+	++	+	1.013
9. F. G.	Chronic nephritis; myocar- ditis; asthma	49	♀	28	0.153	33	200/130	Normal.....	+	++	++	1.021
10. R. J. B.	Chronic nephritis; myocar- dial weakness	65	♂	47	.....	30	160/70	.....	++	++	++	1.019

<sup>\*</sup> Cent nodules below costal border in midclavicular line.

TABLE 4—RESULT OF TESTS IN CASES OF CHRONIC INTERSTITIAL NEPHRITIS WITH HYPERTENSION

Case	Diagnosis	Age	Sex	Blood Nitrogen Mg. per 100 c.c. of Blood	Blood Sugar Gm. per 100 c.c. of Blood	Phtha- lein Elimi- nation % in 2 hrs.	Blood Pressure	Eye-Grounds	Albumin	Casts	Sp. Gr.
1. W. P.	Chronic interstitial nephritis	65	♂	26	0.120	35	180/130	.....	+	+	1.025
2. L. L.	Chronic interstitial nephritis	55	♀	29	0.082	43	225/110	.....	+	+	1.021
3. P.	Chronic interstitial nephritis	55	♂	43	0.106	.	210/150	.....	+	+	
4. G. C. B.	Chronic interstitial nephritis	40	♂	43	0.075	48	185/136	.....	+	+	1.015
5. M. W.	Chronic interstitial nephritis	38	♀	43	0.123	19	256/163	.....	++	+	1.013
6. Mr. R.	Chronic interstitial nephritis	27	♂	67	0.117	18	210/130	.....	++	++	1.009
7. S. R.	Chronic interstitial nephritis	26	♂	56	0.123	22	205/150	Disks edematous, Hemorrhages	++	++	1.013
8. E. B.	Chronic interstitial nephritis	43	♂	46	.....	16	155/110	.....	+	+	1.014
9. E. H.	Chronic interstitial nephritis	21	♀	35	0.07	40	210/115	Edema, Vessels full and dark. Patches of exudate	+	+	1.008
10. P. F.	Chronic interstitial nephritis	61	♂	39	0.074	24	190/110	Nephritis, hemor- rhages, sclerosis	++	++	1.019
11. M. L.	Chronic interstitial nephritis	53	♀	36	0.082	37	170/135	Vessels sclerotic, Nen- tic choroidal changes	+	+	1.013
12. C. B.	Chronic interstitial nephritis	40	♀	....	0.146	10	250/160	Retinitis, Hemor- rhages	++	++	1.015
13. B. W.	Chronic interstitial nephritis	22	♀	33	0.085	60	205/170	Sclerotic changes....	+	—	1.009
14. S. B. J.	Chronic interstitial nephritis	43	♂	50	0.088	37	242/162	Marked sclerosis....	+	+	1.017
15. McC.	Chronic interstitial nephritis	66	♂	58	0.08	75	178/95	Vessels full, Hemor- rhagic exudation	+	++	1.021

confirm those of Rowntree and Fitz,<sup>5</sup> in that there is practically no increase in waste nitrogenous products provoked by such congestion per se; although Strauss and Hohlweg<sup>6</sup> state that this factor is responsible for a moderate increase in these products. See Tables 1 and 3.

In our series of cardiorenal cases, in many of which chronic passive congestion was very evident, only one presented a rise in blood nitrogen. To be of real value in therapy and prognosis, we believe that the test should be repeated at intervals, that due consideration should be given the time and the amount of protein intake, and finally, that each test should be accompanied by a determination of the phenolsulphonephthalein elimination. When both the clinical picture and these details are observed, the value of the test cannot be disputed.

In Table 3, it will be noted that of the cardiorenal group investigated, the absence of retained nitrogen is striking when contrasted with Table 4, in which cases of pure chronic interstitial nephritis with hypertension are considered. In the latter group, eleven out of fourteen cases show evidence of retention, and it is this same group in Table 2 which illustrates a marked reduction in tolerance for proteins as noted above. Certain it is that excessive amounts of nitrogen in the blood afford an index of renal functional capacity. The significance of these results in the pure nephritic cases, however, both from the prognostic and therapeutic point of view, will be dealt with later.

## II. THE RELATION OF NITROGEN RETENTION TO RENAL FUNCTION AS DETERMINED BY THE PHENOLSULPHONEPHTHALEIN ELIMINATION

The technic of the phenolsulphonephthalein test used was that originated by Rowntree and Geraghty.<sup>7</sup> Before discussing the results in our three groups of cases, it may be advisable to note certain conditions under which marked variations in the phtalein output occur. These are:

1. Chronic passive congestion.
2. Various stages of nephritis.
3. Hyperpermeability.

1. *Chronic Passive Congestion.*—Several workers have shown that marked chronic passive congestion greatly decreases the phenolsulphonephthalein output and that as the circulation improves, the output

5. Rowntree, L. G., and Fitz, R.: Studies of Renal Function in Renal, Cardiorenal and Cardiac Diseases, *THE ARCHIVES INT. MED.*, 1913, xi, 258.

6. Strauss and Hohlweg: Quoted by Rowntree and Fitz, *THE ARCHIVES INT. MED.*, 1913, xi, 278.

7. Rowntree and Geraghty: *Jour. Pharm. and Exper. Therap.*, 1910, i, 579.

rises if there is no coexisting renal involvement.<sup>8, 9</sup> This fact may well be utilized in determining the relative responsibility of heart or kidney in the troublesome symptom complex, cardiorenal disease, as successful therapy in this condition rests largely on our knowledge of the underlying causative factor.

2. *Various Stages of Nephritis.*—Phenolsulphonephthalein elimination varies during the course of the illness (nephritis), a fact well established and one which we have frequently observed. Our most striking example of this is Case 4 in Table 5, in which the phenolsulphonephthalein rose from 17 per cent. to 70 per cent. in five weeks, and in which there was no marked evidence of cardiac disease. The patient's improvement paralleled this rise. We freely concede that a rise as marked as this in so short a time cannot be an index of the actual degree of change in renal tissue, but that it is rather an illustration of the fluctuation in functional capacity during the course of the illness. Thus again, if the phenolsulphonephthalein test is repeated at intervals, its value from the point of view of prognosis is evident. We believe that too much emphasis should not be laid on one phenolsulphonephthalein elimination, and in the differentiation of nephritis from chronic passive congestion, it would seem that a series of both phenolsulphonephthalein and nitrogen tests should be carried out in order to reach any definite conclusions.

3. *Hyperpermeability.*—In the past year, Pepper and Austin<sup>10</sup> have called attention to the existence of cases of nephritis in which the functional capacity of the kidney is normal or even above normal. Baetjer<sup>11</sup> has described such cases and considers that there may be a stage in nephritis when hyperpermeability exists at least to phenolsulphonephthalein and some other substances. We have also noted a few cases, but so far the opportunity for serial studies of them has not been presented. It may be that this so-called hyperpermeability is merely an illustration of the possible existence of damaged kidneys with normal functional capacity, at least for some substances. Cases of this type are usually accompanied by chlorid retention.

In our series of pure nephritis of the chronic interstitial type, several interesting facts may be noted (see Table 4). Nearly every case showed retention of nitrogen, decreased phenolsulphonephthalein elimination and high blood-pressure, while the blood-sugar was slightly

8. Farr, C. B., and Austin, J. H.: Jour. Exper. Med., 1913, xviii, 228.

9. Rowntree, L. G., Fitz, R., and Geraghty, J. T.: The Effects of Experimental Chronic Passive Congestion on Renal Function, THE ARCHIVES INT. MED., 1913, xi, 121.

10. Pepper and Austin: Am. Jour. Med. Sc., 1913, cxlv, 254.

11. Baetjer, Walter A.: Superpermeability in Nephritis, THE ARCHIVES INT. MED., 1913, xi, 593.



TABLE 5.—RESULT OF THE STUDY OF A SERIES OF CASES OF CHRONIC PARENCHYMATOUS NEPHRITIS

Case	Diagnosis	Age	Sex	Blood Nitrogen Mg. per 100 c.c. of Blood	Blood Sugar Gm. per 100 c.c. of Blood	Pythia- tein Fili- nation % in 2 Hrs.	Blood Pressure	Eye-Grounds	Edema	Liver	Albu- min	Casta	Sp. Gr.
1. A. S.	Chronic parenchymatous nephritis	22	♀	....	0.095	27	140/90	.....	++	—	++	++	1.013
2. W. M.	Chronic parenchymatous nephritis; weakness myocardial	24	♂	83	0.072	20	98/65	Related retinal veins	++	—	++	++	1.028
3. A. K.	Chronic parenchymatous nephritis	25	♀	74	.....	7	170/130	Normal.....	++	—	++	++	1.019
4. F. A.	Chronic nephritis.....	24	♀	36	.....	17	115/70	Normal.....	+	—	+	+	1.031
5. S. G.*	Chronic parenchymatous nephritis	20	♀	81	.....	5	145/110	.....	++	—	++	++	1.020
6. J. McV.	Chronic parenchymatous nephritis	47	♂	145	0.087	0	140/80	.....	+	4 cm.	++	++	1.012

\* At autopsy the kidneys were found to be secondarily contracted.

above normal in six of the fourteen cases studied. It should be noted that nine of these fifteen patients ranged from 26 to 43 years of age, and that the prognosis was grave in most instances.

Less striking results were obtained in a series of cardiorenal cases as will be seen in Table 3. One case gave evidence of nitrogen retention while the phenolsulphonephthalein varied from 8 per cent. to 45 per cent. The blood pressure was high in three cases, as was the blood sugar.

The series of cases of chronic parenchymatous nephritis shown in Table 5 is too short to permit of definite conclusions.

### III. THE RELATION OF BLOOD-SUGAR, NITROGEN RETENTION, PHENOL-SULPHONEPHTHALEIN ELIMINATION AND HIGH BLOOD PRESSURE

The question of hyperglycemia in high-pressure nephritis is of considerable theoretical interest. Since Neubauer<sup>12</sup> first called attention to this, several workers have confirmed his findings while a few have failed to do so. Thus the present status of blood-sugar concentration in nephritis may be regarded as one of the many points at issue and for that reason is included in these studies. The blood-sugar was determined by the micro method of Bang<sup>13</sup> in which a small amount of blood is required for each test. The blood is obtained by finger puncture, which insures simplicity and the elimination of unnecessary discomfort to the patient. All food was withheld from the patient for at least six hours before the blood was withdrawn. Normal figures by this method lie between 0.06 and 0.1 per cent.

In a former publication, one of us (Hopkins<sup>14</sup>) reported on a study of the blood-sugar in twenty-eight cases of nephritis. Briefly stated, the conclusions to be drawn from that work and the cases here presented are as follows:

A slight hyperglycemia occurs in many high-pressure nephritics and frequently in those with low phenolsulphonephthalein elimination (Table 4). There is no relation between the height of the blood pressure and the degree of hyperglycemia. In most nephritics without high pressure, the blood-sugar is normal. Edema and hepatic congestion do not seem to influence the concentration of blood-sugar (Tables 3 and 4).

Of the eight cases in this series which showed a retention of over 40 mg. of nitrogen, four gave an elevation in blood-sugar. This con-

12. Neubauer: *Biochem. Ztschr.*, 1910, xxv, 284.

13. Bang, I.: *Der Blutzucker*, Wiesbaden, 1913.

14. Hopkins, A. H.: *Am. Jour. Med. Sc.*, 1915, cxlix, 254.

firms the recent work of Borchardt and Bennigson,<sup>15</sup> who also found nitrogen retention a frequent accompaniment of hyperglycemia.

Of the eight cases in which two or three estimations of blood-sugar were made after the various periods of protein feeding, no constant changes were noted.

Alimentary hyperglycemia was pronounced in three out of four cases in which 100 gm. of glucose were fed by mouth and serial tests of blood-sugar made each half hour for several hours.

#### CONCLUSIONS

1. Protein feeding in nephritis has a direct influence on the retention of nitrogen in the blood. This is most pronounced in the pure chronic interstitial type with hypertension.

2. The estimation of retention by blood analysis is of definite clinical value from the point of view of therapy, and though this series is too limited to permit of definite conclusions with regard to its prognostic value, our findings so far confirm those of other workers who advocate its usefulness in this field.

3. Chronic passive congestion does not cause an increase of waste nitrogenous products in the blood.

4. In the presence of nitrogen retention, the phenolsulphonephthalein output is usually low and the blood pressure frequently high.

5. Chronic passive congestion may greatly impair the phenolsulphonephthalein output. Variation in the elimination of this dye may also be noted in different stages of nephritis, and in cases with "hyperpermeability."

6. To be of value, the nitrogen retention and phenolsulphonephthalein tests should be repeated at intervals, the value of the former being increased when combined with clinical observations of the patient, diet, etc.

7. A slight hyperglycemia occurs in many high-pressure nephritics and frequently in those with retention of nitrogen and impaired phenolsulphonephthalein elimination.

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15. Borchardt, L., and Bennigson, W.: *München. Med. Wehnschr.*, October, 1913, p. 2275.

# A STUDY OF GENERAL AND LOCALIZED EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN IN CASES OF HUMAN CANCER \*

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## I. INTRODUCTION

In several brief communications<sup>1</sup> we published previously our observations on the effect of intravenous injection of colloidal copper in patients suffering from cancer. We also referred to experiments in which we used solutions of casein. We limited ourselves on those occasions to a brief report of some of our conclusions and referred to our future more detailed publication for a discussion of various results and problems of which we could not treat in our preliminary notes. In the following more complete report we shall especially analyze the relation between various sets of general and local effects of the injection of colloidal copper and casein, and the effect of these substances on the tumors. We shall compare the actions of solutions of colloidal copper with those of casein, and the effect of these substances in patients and in animals inoculated with carcinoma.

Our investigations were the outcome of preceding studies on the action of various sets of substances on animal tumors.<sup>2</sup> We wish here only to refer to a few of our results. We found that various sets of substances, as colloidal metals, certain protein substances and herudin, cause an inhibition or retardation, and in some cases a retrogression, of a certain number of tumors. Through a combination of several substances the effect of a single substance could be much increased. The efficacy of these substances depended especially on the age of the tumors, very young tumors being much more resistant to an inhibiting effect. Of special interest seemed to us the proof that repeated injections of these substances call forth in the injected animals processes of reaction against the injected substance.

These reactions have a double origin, being dependent on changes taking place (1) in the organism of the injected animal, and (2) in

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1. Interstate Med. Jour., 1912, xix, No. 12; 1913, xx, Nos. 1 and 5; Jour. Am. Med. Assn., 1913, lx, 1857.

2. Loeb, Leo, and Fleisher, M. S.: Jour. Am. Med. Assn., 1913, lx, 1857; Fleisher, M. S., and Loeb, Leo: Jour. Exper. Med., 1914, xx, No. 5.

the tumor cells themselves. Thus an immunity of double origin becomes established. The immunity dependent on changes in the tumor cells can be transmitted to successive generations of tumor cells. The immunity thus established tends to prevent the continued effect of the various substances and to make it transitory. The immunity is a specific one; animals and tumors immunized against colloidal copper are immune against colloidal copper, but not against herudin and vice versa.<sup>3</sup>

We had intended to limit our work entirely to animal tumors, being doubtful as to whether animal experiments had advanced sufficiently to permit an extension to the field of human cancer, and it was only at the urgent request of physicians that we undertook our work on patients. While in the course of this work we observed marked improvement in the case of some patients, we stated from the beginning that our work was of an entirely experimental character, and we warned against its use in general practice, and very soon afterward we expressed the opinion that even in the most favorable cases a cure could not be expected through this kind of treatment.

While we thus rated the significance of these experiments from the point of view of direct applicability in the treatment of cancer as not very high, we believe that from the point of view of theoretical interest our observations make a more detailed publication advisable.

## 2. METHOD OF PREPARATION OF THE SOLUTION OF COLLOIDAL COPPER AND OF CASEIN AND TECHNIC OF INJECTION

For the preparation of colloidal copper we employed Bredig's method, at first, however, making use of an alternating current. Later we used a pulsating direct current obtained by means of a mercury arc rectifier. This passes through twenty-three large lamps of 32-candle power and five small lamps of 16-candle power; the wires terminate in copper electrodes 4 mm. in diameter. These are inserted into a beaker containing 1,500 to 2,000 c.c. of water, twice distilled. The water is first boiled to expel air and used after it has cooled. We used a current of 60 volts and from 16 to 18 ampères. The two electrodes are first brought into contact with each other and then gradually separated so that a spark is drawn out. When the passing of the spark stops, it is necessary to touch the wires again, separating them afterward gradually. This must be repeated again and again. We find it very convenient to attach one wire to an electric bell which keeps oscillating and drawing out sparks continuously. It is best to steam the beakers before using them the first time.

3. The possibility of an immunity against the action of the injected substances acquired through a relatively limited number of injections had been foreseen at an early stage of our work, and determined to a great extent the plan of our experiments. The same possibility we had in mind when we undertook our experiments on human cases and I expressed repeatedly in the beginning of our work the opinion that processes of immunization might prevent a continued efficiency of substances even in those cases which at first seemed to be beneficially influenced; I warned, on the basis of these considerations, against drawing definite conclusions as to the effect of these substances.—Loeb.

The copper wires must be cleaned each time with sandpaper before they are ready for use.

*Preparation of Various Casein Solutions.*—We used different casein preparations, purified as well as non-purified preparations. Into some casein solutions sulphur was introduced, with a view of possibly increasing the efficiency of the preparation. The effects of the various solutions were, in the main, due to the presence of the casein. Solutions prepared with commercial (impure) casein showed approximately the same effects as solutions prepared with purified casein. Addition of flowers of sulphur did not essentially modify the character of the solution. Solutions, however, into which sulphur had been introduced in the form of hydrogen sulphid (Solution 4 and Solutions 4, 16 and 13) were often more poisonous; it is probable that in such cases small quantities of hydrogen sulphid were left in the solution and caused some of the complications which were occasionally observed. The majority of the solutions contained about 1 to  $1\frac{2}{3}$  per cent. casein.

*Technic of Injection.*—The technic used in giving intravenous injections of colloidal copper and casein is about the same as that used for injecting salvarsan, except that in the case of colloidal copper and casein it is unnecessary to use normal salt solution either in the beginning or at the end of the injection. A No. 24 Burroughs-Wellcome needle was generally used in our work. We used a pressure apparatus<sup>4</sup> which eliminated all waste of time and enabled the operator to inject as many as twenty-three patients in six hours, two patients being injected at the same time. This apparatus consisted of a reservoir containing the solution to be injected, two dosage containers and a drum for compressed air. The amount of pressure was regulated by a mercury manometer. The fluid in the dosage containers was kept at a constant temperature by an electric stove regulated by a thermostat, which kept the temperature constant within one-fifteenth of a degree. With this apparatus we were able to keep temperature and pressure constant. The pressure we used depended on the way the patient stood the injection, on the size of the veins and on the amount of fluid to be injected, and was regulated accordingly.

### 3. EFFECT OF THE INJECTIONS OF COLLOIDAL COPPER AND OF CASEIN ON THE VEINS

It is of practical as well as theoretical interest to analyze the effect of the injections of casein and colloidal copper on the walls of the veins with which the injected fluid came into contact after injection.

We consider especially here the pathological changes taking place in the injected veins. The following facts concerning these changes may prove of interest:

1. Injections of casein solutions were tolerated by almost all patients without any resulting changes in the veins. In two cases, however, even the casein had an injurious effect on the veins; both of these cases were in old men, in whom also the colloidal copper had a very marked effect on the veins. In contradistinction to casein, the injection of colloidal copper caused some changes—sometimes very slight and transitory, sometimes very marked and permanent—in the majority of patients. We may therefore conclude that colloidal copper,

4. This apparatus was devised by Dr. W. O. Sweek and made by F. F. Dietz.



and probably also other colloidal metals, cause, in contact with the wall of the veins, pathological changes.

2. In general we can say that the more intimate the contact of the colloidal particles of metal with the wall of the vein, the more marked were the changes.

3. The frequency with which a vein could in the same area be injected with the colloidal copper differed very much in different individuals. In general we can state that frequent repetition of the injections, therefore of the action of colloidal copper, leads to changes, even in cases in which a single injection is without apparent effect. The time required for an affected vein to enable it to return again to its approximately normal condition differed in the case of different individuals.

We may assume that in every case some changes take place in the wall of the vein as a result of the contact with the colloidal copper. In some cases, however, they are very marked, while in others they are very slight. But even in the latter frequent repetition of the injections at a time when the vein had not yet resumed its normal condition leads to a summation of the pathological changes.

4. The changes themselves consist evidently in an injury to the endothelial cells, which makes the latter more permeable to fluid constituents of the blood. Fluid parts of the blood are therefore liable to infiltrate the vessel-wall and the neighboring tissue and make the vein hard and swollen. It is also probable that some of the colloidal particles of copper in some cases enter and irritate the surrounding tissue and then cause a dilatation of the vasa vasorum, thus producing redness of the area surrounding the vessel-wall. Occasionally, the permeability of the vessel-wall may become so markedly increased that edema of a part of the injected extremity follows. Colloidal copper acts, therefore, in this case similarly to certain substances which are supposed to cause, after intravenous injection, edema as a result of injury of the endothelium (as for instance arsenic preparations).

5. It is of great interest that the reaction of the vascular endothelium to injurious influences seems to depend on a sensitiveness variable in different individuals. Even if we allow for differences in the size of the veins, in the rapidity of the flow of the solution in the vessels, in age and general condition of health of the person, there remains usually a factor which points to individual differences. On the whole the veins of strong men are usually more resistant to the injurious effect of the colloidal copper than the veins of emaciated and weak patients; but we found strong men with large veins whose veins proved very sensitive toward the contact with colloidal copper, and, while weak and emaciated women have usually less resistant veins

than strong young women, some old and emaciated patients had resistant veins. In addition, it is probable that a kind of work leading to marked development of the muscles of the arms tends to make the veins more resistant. Two persons whose veins had been most resistant to the action of colloidal copper had both been blacksmiths.

#### 4. GENERAL EFFECTS OF THE INJECTIONS OF COLLOIDAL COPPER AND CASEIN

##### I. QUANTITIES INJECTED

We started usually with relatively small doses of colloidal copper and of casein and gradually increased the quantities injected, using the general reactions following the injection as an indicator of the rate at which the dose could be increased. The first dose was usually 100 or 150 c.c. of colloidal copper and in the majority of cases it was gradually raised to 400 c.c.; in some cases much larger doses were injected. The time when the dose of 400 c.c. was reached varied in different cases. If the dose was rapidly advanced it could be reached at the time of the fifth injection; in other cases it was reached between the eighth and twelfth injections. The number of injections given in different cases varied in the majority of cases between twenty-five and seventy-three. In some cases only a total of from thirteen to sixteen injections was given. Usually four or five, in one case three or four, injections were given each week.

In most cases in which casein was used the injections followed a preceding series of injections of colloidal copper; but between these casein injections there was usually interspersed a smaller or larger number of injections of colloidal copper; sometimes the series of colloidal copper injections was directly followed by a casein series, and only in the later period of the casein injections were injections of colloidal copper again interspersed among the casein injections. In some cases the initial series of copper injections consisted of more than twenty-five, in other cases of only five injections; the number of copper injections interspersed with those of casein also varied in different cases. In one case there was first given a series of casein injections and later some copper injections were given alternately with the casein injections. The amount of casein given in each injection varied much in different cases. Especially, however, in the later period in our work we chose very small initial doses, somewhere between 2 and 5 c.c. In other cases, especially in the earlier period, as much as from 11 to 25 c.c. were chosen as the initial doses, and in some cases even larger initial doses had been given. While some persons could stand these latter quantities comparatively well, in others an extremely strong reaction followed. Gradually in the course of

treatment the doses were increased, in some cases to a maximum of 25 c.c., in others to 50 c.c.; in still others to 90 c.c., and in one patient as much as 155 c.c. were given in one injection. This same patient also received twice at the same injection 200 c.c. colloidal copper immediately followed by 50 c.c. of casein. The number of casein injections given to the individual patients varied very much. Some patients received as many as 48, 46, 36, 32 and 31 injections, others received only between 15 and 21, and still others only a few injections. In most cases two or three injections were given in the course of a week; occasionally there were intervals up to nineteen days between two injections, and in some patients there were, during a certain period, injections given on successive days.

## II. THE EFFECT OF INJECTIONS OF COLLOIDAL COPPER ON THE TEMPERATURE CURVE

Intravenous injections of colloidal copper were usually followed by a rise in temperature. This rise began within the first hour and reached its maximum several hours after the injection. In some cases in which a large quantity of the solution had been injected, the maximum rise was reached from five to seven hours after the injection; the temperature usually became normal again on the day of the injection; but on several occasions the temperature was still abnormal on the day following an injection, without a new injection having been given. Thus in the case of a strong man, following the twenty-third injection the temperature rose on the day of the injection to 100 F., and on the following day the temperature was still 99. In this case no complications (as, for instance, an infection) were present which could have explained the rise on the second day. In other cases there was, however, especially in the later stages of the disease, sometimes an infectious process present as a complication which in itself caused a rise in temperature, and to which the rise in temperature caused by the injection was added. In such cases we found a rise in temperature even on days on which no injection had been given.

An analysis of the various cases shows the following factors to be of importance in determining the extent in the rise of temperature observed:

1. The quantity of fluid injected. On the whole we can say that the larger the quantity injected the greater the rise.
2. This factor is, however, complicated by a second factor which, during the period of the later injections, tends to counteract the gradual rise in temperature which should be expected in accordance with the gradual increase in the doses; namely, an immunity which is gradually established as the result of the injections; we shall consider this factor

separately later on. The gradual production of an immunity during the course of the injections makes it necessary to compare in the different cases the effect of the first injections on the temperature. If we do this we notice then that

3. There are individual differences in different patients as far as the rise in temperature is concerned. In some cases the temperature after the first few injections rose hardly at all or not higher than a little above 99 F., and only rarely to 100. This effect we found especially, but not exclusively, in relatively strong persons; in a few rather old and not very strong patients the general reactions were also relatively slight. In a considerable number of cases the rise varied approximately between 99 and 100 F. This class includes a number of weak as well as of strong persons. In a third class, not quite so numerous as the others, the rise varied between 100.5 and 102. This class included mostly weak persons. We find, therefore, as the third factor, individual characteristics, among which the physical strength of a patient seems to be of great importance.

4. In regard to some accidental factors we cannot speak with the same degree of certainty. It seems, however, that some variations in the temperature of the injected fluid (too low a temperature causing higher fever) variations in the size and number of colloidal particles in a volume unit of fluid and perhaps the rapidity of injection had, in some cases, some influence on the degree of fever. We also noticed that if on two successive days the same amount of solution was given, there was occasionally a more marked rise on the second day. We have in such cases possibly to deal with a summation of effects, which, however, cannot consist in a summation of the fever curves, the temperature being usually normal on the day following an injection; but it may consist in a summation of changes somewhere in the body indirectly connected with the rise in temperature. Bacteriological examination of the solutions of colloidal copper proved them to be sterile. The rise in temperature following the injections can therefore not have been due to admixture of bacteria.

### III. IMMUNITY ACQUIRED AGAINST THE EFFECT OF COLLOIDAL COPPER ON THE TEMPERATURE

The rise in temperature which followed the injections of colloidal copper became generally less, the larger the number of injections given; this applies to all classes of persons, as well to those in whom the reaction had at first been very marked, as also to those with a reaction of medium strength in the beginning, and to those in whom from the beginning the reaction had been weak. While in the first

two classes the acquired immunity could be easily demonstrated, inasmuch as notwithstanding the larger doses given at later periods the rise in temperature became less, in the last class the establishment of an immunity could be assumed on the strength of the fact that the larger doses given later did not cause a more marked, or even caused a somewhat weaker, reaction than the first smaller doses. In no case was the immunity absolute. There were usually some injections which caused, again, a more marked rise in temperature. In some cases in which at first the reaction had been very marked, it was almost entirely absent in the later periods, while in other cases the difference between the first and later reactions, although present, was not so marked; in these cases the transition from the not immunized to the immunized state was more gradual. In a few cases no definite immunity could be shown to exist. While in some cases this was due to the appearance of complicating processes tending in themselves to raise the temperature, in a few exceptional cases no immunity was apparently produced. In some cases partial immunity became noticeable as early as after the fourth or fifth injection; in others it required from ten to twelve; in still others from fifteen to sixteen injections, before the immunity became marked. After the first sixteen injections the immunity became usually especially marked.

The immunity produced against the general effects of colloidal copper is not specific. It can also be produced through preliminary injections of solutions of casein which on their part cause a marked rise in temperature. We found that in patients in whom, after a series of injections of colloidal copper, a series of injections of casein was given, and in whom after a number of casein injections again a large dose of colloidal copper was injected, the injection of colloidal copper was either followed by no fever reaction at all or by a much slighter reaction than those observed previous to the injections of casein. It appears even probable that many conditions giving rise to a transitory elevation of temperature may thereby lessen the general effects of colloidal copper. In such cases we may have to deal with a lessened excitability of certain nervous mechanisms as a result of previous stimulations.

#### IV. SOME OTHER EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER

Besides the rise in temperature, the most common effect following the injections of colloidal copper was a chill; in most cases beginning about thirty minutes (twenty to sixty minutes in individual cases) after the injection. It lasted usually about half an hour. The presence and intensity of the chill depended, in the same individual, on the

height in the rise of the temperature following the injection. There was a correspondence in the same individual between the severity of the chill and the temperature curve. There was, however, a great difference between different individuals in the liability of a chill to follow the injection. In one patient, a strong man, in whom the temperature showed only slight rises after the injections, there was usually a marked chill present; also at times when the rise in temperature was almost absent. In another patient, an old man, in whom also the rise in temperature was usually slight, a chill was only once observed, viz., after the twenty-fourth injection, when the temperature rose to 100. In typical cases a slight chill seemed to correspond to a rise in temperature to about 101, while a severe chill followed a rise to 102 or higher. In other persons, however, there was a slight chill when the temperature went up to 100, and a severe chill when the temperature went up to 101 or higher; this was the case, for instance, in a girl 16 years old. There were occasionally some other symptoms present; but in most cases they were only exceptionally noticed and found only on occasions when the temperature rose somewhat higher than usual. Such isolated occurrences were: an attack of dizziness, perspiration and symptoms of syncope, pain in head and back, abdominal cramps and vomiting. Other symptoms were on several occasions observed in an old man of strong build. Here the injections were followed by weakness, irregular pulse and vomiting. In an otherwise strong young girl the injections were regularly followed by headache and pain in the arms. When the temperature remained below 100 there was usually no chill, but slight headache and pain in one or both arms were observed.

#### V. THE EFFECT OF INJECTIONS OF CASEIN ON THE TEMPERATURE CURVE

During the first period the temperature following an intravenous injection of casein was higher than after the copper injection during the corresponding period. This holds good even in cases in which small doses (from 2 to 4 c.c. of the solution) were used during the first injections. In the majority of cases the maximal temperature after the first three or four injections varied between 101 and 104. In some cases it was still higher; in some resistant persons, especially persons of strong build, it did not reach 101. The fever curve after these injections had a steeper course than after injections of colloidal copper, at least in those cases in which large quantities of colloidal copper were injected; the maximum temperature was usually reached earlier than



after injections of colloidal copper, viz., between one and one-half and three hours after the injection; after five or six hours the temperature became usually normal or almost normal again. In some cases, however, in which with the first injections relatively large doses were given, or in which the patient was very sensitive to the casein, the temperature remained high even for considerably longer than a day. In a patient, e. g., in whom, after the first injection the temperature rose on the first day to 105.4, the temperature returned to normal only on the twelfth day after the injection. There seemed to be an individual difference in different individuals, as to the time required in which, after about the same maximum had been reached within a few hours, the temperature returns to the normal point. We must assume that in those cases in which the temperature remains high during a long period, unchanged or only slightly changed casein is circulating in the blood, while in those cases in which smaller doses were given or otherwise the body was normally able to split or eliminate the casein more rapidly, the temperature becomes more rapidly normal. We see accordingly that a long-continued rise in temperature is especially noticeable following one of the first three injections, while later, when a certain immunity has been reached, the return to the normal point is usually more rapid, although the doses given may be much higher than at first. In one person, in whom the temperature remained high during several days, and in whom we gave special attention to this point, the temperature during the afternoon was found to be from 0.2 to 0.6 higher than in the morning.

On the whole the same factors which determined the rise in temperature after injections of colloidal copper are also of importance in the case of casein. The immunity acquired in the course of these injections we shall discuss separately. The size of the doses given determines to a great extent the rise of the temperature. But there remain, besides, individual factors. If we compare several persons who receive in the first injection approximately the same doses, the severity of the reaction is not the same. Thus in one person in whom the injections of colloidal copper caused only very little rise in temperature, casein solutions caused also relatively slight changes in temperature. Here also some strongly built patients seem to be more resistant than weaker persons. Larger initial doses which one patient tolerates with only moderately severe reaction, may cause in another person reactions of a very great severity. If 2 c.c. were given as the initial dose and during the first three or four injections the dose was not increased more than 1 or 2 c.c. each time, only relatively slight or moderately severe reactions were observed.

VI. IMMUNITY ACQUIRED AGAINST THE EFFECTS OF CASEIN ON  
THE TEMPERATURE

Just as after injections of colloidal copper, an immunity against the effects of casein was produced through repeated injections. In the typical cases we can distinguish three periods in the process of immunization. The first definite signs of immunity became noticeable at the time of the fourth injection about eight days after the beginning of the injections. Then there followed an intermediate period lasting from the fourth to the twelfth or twenty-second injection, during which, notwithstanding the larger doses of casein, the temperature was  $1^{\circ}$  or  $2^{\circ}$  lower than in the beginning. This period was followed by a third period comprising the later injections in which, notwithstanding the still higher doses given, the rise in temperature was still more reduced, and in some cases not rarely remained normal after the injections, while occasionally there was a slight rise to 99 or 100, which in a few cases might have been greater. In other cases, however, in which the doses were increased more rapidly, the early onset of the immunity after the first three injections was not so clear. In a strong man, for instance, immunity became clear only after the first twenty injections. Notwithstanding the higher doses given, the temperature was now, on the average, less than after the former injections. In a strong girl 16 years old in whom the fever reaction following the injection was usually very marked, a definite immunity was established only after about thirty-six injections, three months after the beginning of the administration of casein. Immunity becomes established not only in strong, but also in weak persons in whom metastases are present in internal organs at the time of the treatment. In our cases we had of course to deal with the complication consisting in the gradual increase in the doses of casein given. It was therefore possible that in a certain case the immunity existed at a time when the temperature reaction did not decrease in the course of the successive injections, but in such cases the immunity became apparent through the lack of increase in fever in successive injections, notwithstanding the increase in the doses given; the immunity established was in no case absolute, but only partial.

In some cases there was an interval varying between ten and nineteen days between two successive injections. It was of interest to determine whether the injections following the interval would be accompanied by signs of an anaphylactic reaction. While on two occasions it can be definitely stated that such a reaction did not occur, the reaction being not more marked after the injection following the interval than after the preceding injection, on two other occasions the injection following the interval caused relatively severe symptoms.

In those cases in which an anaphylactic reaction can be definitely excluded, we may assume that the quantity of casein given in the course of the preceding injections had been too great to make possible the establishment of anaphylaxis within a relatively short interval of time.

While as we saw, previous injections of casein cause a marked decrease in the general effects following the injections of colloidal copper, the converse condition does not hold good: Preliminary injections of colloidal copper do not protect against the general effects of casein. In this connection we must remember that injections of casein caused very much more marked general reactions than colloidal copper.

If we compare the curve of immunization produced through injections of colloidal copper with the curve resulting from injections of casein, we see on the whole a definite parallelism as to the time when the immunization first becomes apparent and when it becomes more marked.

#### VII. OTHER EFFECTS FOLLOWING INTRAVENOUS INJECTIONS OF CASEIN SOLUTIONS

Other symptoms besides temperature were more severe after casein than after colloidal copper injections. A chill beginning from thirty to forty-five minutes after the injection and lasting about half an hour was a very common symptom after use of casein as well as of colloidal copper. In the same individual there was on the whole a parallelism between the severity of the chill and the height of the rise in temperature following the injection; frequently a temperature below 101 F. was preceded by a relatively slight, a temperature of 102 or more by a severe, chill. But in the same individual the correspondence between height of rise in temperature and severity of chill was not complete. We find here again a similar difference between individuals as we found in the case of colloidal copper. Some persons were inclined to have a chill after injection of colloidal copper as well as of casein, even in the case of only a slight rise in temperature; in other persons after administration of copper, as well as of casein, a higher temperature was required than in others to produce a chill. When there was a marked rise in temperature, perspiration was not infrequently observed, and after the maximum of the fever had been reached, pain in the region of the stomach and vomiting occurred in a number of cases. These latter symptoms followed much more frequently injections of casein than of colloidal copper. It seems probable that the injection of casein causes contraction of the stomach. A very common symptom after injections of casein was pain in the back; it started often before the injection was finished. This symptom appeared more frequently

in some patients than in others. In some severe cases there was pain over all parts of the body, but sometimes especially localized around the tumor. Thus in a patient with a lesion in the right humerus the arm was affected; in others the face, if the lesion was in the face. In a patient with metastases in the liver, after an injection of a relatively large dose of casein, severe pain in the liver region appeared. In some cases pain around the seat of the lesion was present even if the rise in temperature was very slight. In a few cases this localized pain, appearing about one hour after an injection, was the most persistent symptom next to the rise in temperature. After large doses followed by marked general effects, pain around the tumor may be present one or several days after the injection. In a few cases injections of casein were followed by cardiac and respiratory disturbances: cyanosis, weak irregular pulse and rapid, shallow respiration; in such cases the temperature was usually high, for instance 104.6 in one case. While such attacks were, on the whole, exceptional occurrences, in one or two patients irregular pulse following the injections was a more frequent symptom. It is possible that some heart lesion existed in such patients.

There remain a few exceptional symptoms to be mentioned, viz., herpes labialis, which followed the injection of casein in two cases on occasions when a marked rise in temperature was present. In one patient the twenty-first injection was followed by an erythematous eruption of the skin. On the whole, those casein preparations which caused a more marked rise in temperature caused also more severe other symptoms. With increasing immunity the other symptoms gradually disappeared simultaneously with the fever. In a few cases one of the first three injections was, as mentioned above, followed by very severe symptoms. In these cases, too large doses had been given.<sup>5</sup> It concerned four patients who received the injection at about the same time. The following case may be cited in detail:

CASE 1 (No. 3614).—Multiple carcinoma of face and neck. The first injection of 15 c.c. casein was followed by slight symptoms. At the time of the second injection almost 30 c.c. were given. During the injection there was severe pain in the back. For a period of one-half hour there was, every five minutes, a convulsion lasting two or three minutes; the face was red, breathing irregular, pulse rapid. Thirty minutes after the injection there was a severe chill lasting from twenty-five to thirty minutes, followed by a rise in temperature to 106 F., reached five and one-half hours after the injection; delirium and anuria were present, and lasted twenty-four hours. The following twelve days the patient was unable to eat, he lost weight and felt weak. After two weeks he began again to gain in weight and was normal at the end of six weeks. We shall have occasion later to refer to the effects of these injections on the tumor.

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5. This was an accidental happening during an unavoidable absence of one of us.

## 5. EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND OF CASEIN ON THE BLOOD

### 1. EFFECT OF THE INJECTIONS OF COLLOIDAL COPPER ON THE NUMBER OF ERYTHROCYTES

We can divide the patients in four categories:

1. In some patients there was a decrease in the number of erythrocytes caused by the injections. This decrease was, however, not very great. Thus, in one well-built patient the number of erythrocytes diminished in the course of ten injections from 5,100,000 to 4,400,000. This decrease is relatively slight. In some cases it is confined to the first period of injections, and in the course of the later injections the number may again increase. In other cases there is a decrease also during the later injections, but after completion of the series of injections a recovery takes place.

2. In some patients in whom anemia was present from the beginning, the anemia progressed during the course of injections, but the decrease in erythrocytes was not more marked than could be expected as a result of the disease. These were patients in whom there were large suppurating or putrid, ulcerated surfaces.

3. In some other cases there was no noticeable decrease, and this applied mostly to less advanced cases, but it was also found in a patient who had at the beginning of the injections 2,100,000, and after a series of fifteen injections 2,200,000 erythrocytes.

4. In one case we found a distinct increase during the course of injections. This was a patient with a carcinoma affecting the orbital cavity and its environment. At the beginning there were 3,700,000. One and one-half months later 4,200,000 and two and one-half months later 4,900,000; nine days after the last (seventy-third) injection, more than three months after the beginning, 5,200,000; three and one-half months after the last injection 6,420,000; six and one-half months after the last injection 4,300,000 erythrocytes. This was the case of a strong man who received very large quantities of the solution at each injection. The maximum was 1,200 c.c.

In some cases we made a count directly before an injection as well as a few hours later. In such cases we found usually a very slight decrease in the number of erythrocytes after the injections.

We may therefore conclude that after the injections of colloidal copper a certain number of erythrocytes are destroyed; that in some cases the reparatory changes which take place suffice to replace the lost red blood corpuscles. Such reparatory processes may occur even in very anemic persons in whom a destruction of erythrocytes took place as the result of other injurious influences, which latter loss the blood-

forming organs were not able to repair. In some cases the reparatory processes are not quite strong enough to keep the number of erythrocytes at the normal level. In such cases the reparatory processes may, however, after cessation of the injections, be strong enough to replace the lost erythrocytes.

## II. EFFECTS OF INTRAVENOUS INJECTIONS OF CASEIN ON THE NUMBER OF ERYTHROCYTES

Injections of casein did not usually produce any noticeable decrease in the number of erythrocytes. While possibly in some cases a severe reaction following casein injections may have caused a slight decrease, there was usually no marked difference in the number of erythrocytes at the beginning and at the end of the casein injections. In one case there was even a gain during the period of immunity against the general effects of casein injections. In other cases an increase began to take place after the course of injections had been completed.

In cases in which the disease itself leads to an increasing destruction of erythrocytes, injections of casein cannot prevent the decrease. Intravenous injections of casein have therefore no marked influence on the number of erythrocytes; they neither diminish them very markedly nor do they prevent a decrease produced by other conditions.

## III. EFFECT OF THE INTRAVENOUS INJECTIONS OF SOLUTIONS OF COLLOIDAL COPPER AND OF CASEIN ON THE LEUKOCYTES

A complete study of the effect of these solutions on the leukocytes, including a detailed determination of the number of the various leukocytes following injections in each patient, at different periods of the treatment, could not be carried out. In a few cases, however, the leukocytes were studied at different times following an injection. In most cases only one examination was made following an injection and only after certain injections. We may, however, state that a leukocytosis often follows injections of colloidal copper as well as of casein, and that the leukocytosis following injections of casein is usually more marked than the leukocytosis following the injections of colloidal copper. This corresponds with the higher fever which usually follows injections of casein. The maximum of the leukocytosis seems to be reached somewhere between two and five hours after the injections; eight hours after the injections the number of leukocytes is often again normal. In some cases, however, when the general reactions following the injections of casein have been very severe, and fever lasts longer than twenty-four hours, the leukocyte count may still be high twenty-four hours after the injection. Even many injections of either casein or colloidal copper did not produce a complete immunity against the



effect of these substances as far as the effect on the leukocytes is concerned.

The increase in leukocytes was in the main due to an increase in the number of neutrophil polynuclear leukocytes. It is possible that at the same time there existed also an absolute increase in the number of lymphocytes. In some cases in which there existed a relative increase in the lymphocytes, injections of casein produced only a very slight, if any, increase in the total number of leukocytes, but principally a change in the proportion of different kinds of leukocytes. Thus, in the repeatedly mentioned case of a 16-year-old girl there was, three and one-half months after the beginning of the injections, preceding an injection of casein, 9,800 leukocytes. Of these there were 48 per cent. polynuclear neutrophils, and from 50 to 52 per cent. lymphocytes. Three hours after the injection of casein the number of leukocytes had only slightly increased, namely, to 11,000, but the polynuclears had increased to 74 per cent. and the lymphocytes had decreased 50 per cent., namely, to 25 per cent.

#### IV. A RELATIVE INCREASE IN THE NUMBER OF LYMPHOCYTES PRODUCED THROUGH LONG-CONTINUED INJECTIONS OF EITHER COLLOIDAL COPPER OR CASEIN

The changes in the number of leukocytes mentioned above represent merely transitory changes. It is now of special interest that a large number of injections of colloidal copper or casein, given through a considerable period of time, have, in addition, an influence on the relative number of the various leukocytes, and this influence persists over a long period of time. While the transitory effect consists in an absolute increase in the number of polynuclear neutrophils, the long-continued effect consists in the opposite change, namely, a relative increase in lymphocytes, especially of the small lymphocytes, and a relative decrease of the polynuclear neutrophils. We have observed these changes in all those cases in which the blood examinations were made at intervals through relatively long periods of time. The change became usually distinct about two or two and one-half months after the beginning of the treatment, reached a maximum approximately from three to six or eight months after the beginning and then commenced slowly to decline. This condition lasted, therefore, much longer than the period of injections. It is observed in the following cases:

CASE 2 (No. 3641).—White man, aged 34; multiple carcinoma of the skin. The beginning of the change was noticed somewhat more than two months after the commencement of the treatment and during the period of casein injections. While previously the number of polynuclears had been about 75 per cent., and of lymphocytes 20 per cent., or less, somewhat more than sixty days

after the beginning of the treatment there were 67 per cent. polynuclear neutrophil leukocytes, 27 per cent. small, and 6 per cent. large lymphocytes. About five months after the beginning of the injections of colloidal copper, and three and one-half months after the beginning of the injections of casein, there were 48 per cent. polynuclear leukocytes, 48 per cent. small and 4 per cent. large lymphocytes; the number of leukocytes was increased to 10,800. For the next two or three months the count remained approximately the same, although the total number of leukocytes returned to normal. This change was still present, but perhaps slightly less marked eight and one-half months after the beginning of the treatment and almost two months after the last injection. At that time there were present at two counts made at two days' intervals: polynuclears varying between 48 per cent. and 60 per cent., small lymphocytes varying between 32 per cent. and 48 per cent.; 3 per cent. large lymphocytes, transitional leukocytes varying between 1 and 3 per cent. and eosinophils varying between 2 and 4 per cent. At a count made fourteen and one-half months after the last injection (Aug. 31, 1914) examination of the blood showed the following condition:

Erythrocytes .....	4,720,000
White blood cells .....	15,600
Polynuclear neutrophil leukocytes.....	56 per cent.
Large and small lymphocytes.....	41 per cent.
Large mononuclear cells.....	1 per cent.
Eosinophils .....	2 per cent.

We see, therefore, that this change is not of a transitory character, but persists for a long period of time.

CASE 3 (No. 1436).—Woman, aged 69; carcinoma of face, affecting the ear. Two months after the beginning of the injection there were 68 per cent. polynuclear neutrophil leukocytes, 30 per cent. lymphocytes and 2 per cent. eosinophils present. Two and one-half months after the beginning of the treatment there were 57 per cent. polynuclears and 5 per cent. eosinophils. Three months and nine days after beginning of the treatment there were 57 per cent. polynuclears, 40 per cent. lymphocytes and 2 per cent. eosinophils. Five months after the beginning and thirty-nine days after the end of the treatment there were 48 per cent. polynuclears, 49 per cent. lymphocytes and 3 per cent. eosinophils. One month later the polynuclears had decreased to 45 per cent. and the lymphocytes had increased to 48 per cent.; there were 4 per cent. eosinophils. Nine months after the beginning of the treatment and five months after the completion of the treatment, the lymphocytes had again decreased to 40 per cent., the polynuclears had increased to 52 per cent., and the eosinophils to 2 per cent. Twelve or thirteen months after the beginning and eight or nine months after the completion of the treatment, there was a further rise in polynuclears whose number varied between 58 per cent. and 68 per cent.; there were between 31 per cent. and 41 per cent. lymphocytes (about 16 per cent. of which were large lymphocytes). There were also 1 per cent. eosinophils. Similar observations which do not need to be given in detail were made in the following cases:

CASE 4 (No. 1476).—Man, aged 59. Carcinoma of the cheek.

CASE 5 (No. 1504).—Man, aged 56. Carcinoma of the eyelids extending to the eye.

CASE 6 (No. 1502).—Man, aged 57. Carcinoma affecting the skin in the neighborhood of the eye.

CASE 7.—R. M., girl, aged 16. Swelling in the humerus of the right arm, diagnosed as sarcoma.

In Cases 3 (1436) and 6 (1502) we can attribute the change to the effect of colloidal copper. In Case 6 (1502) no casein had been given. In Case 7 only a few injections of colloidal copper had been given,

and the changes were in all probability due to casein. In the other cases a larger number of injections of both casein and colloidal copper had been given. This relative increase in lymphocytes is at certain times accompanied by an increase in the total number of leukocytes; at other times the latter is absent. We see, furthermore, that old and young, strong and weak persons, can show this change. We have to distinguish such cases from others in which already before the beginning of the treatment a relative lymphocytosis is present.

In some cases it seems that the first changes in this direction were observed from five to eight weeks after the beginning of the treatment; but inasmuch as no continued examinations of the blood were made in these cases, no definite statements concerning the point can be made.

As to the significance of these changes, it is probable that they represent a reaction of the organism toward all kinds of substances administered during a long period of time which cause a rise in temperature and a transitory increase in polynuclear neutrophil leukocytes. But whether this reaction consists in a mere change in the distribution of the various kinds of leukocytes in the superficial and in the deeper blood vessels, or whether we have to deal with an actual new formation of lymphocytes, cannot be decided with certainty at present, although the latter alternative seems to be more probable. It has been observed by Baeslack<sup>6</sup> that there is an increased lymphocytosis present in cancerous animals during the period of retrogression of a cancer. We can exclude with certainty in our cases any relation of the lymphocytosis to retrogressive changes, which latter took place in some cases long before the onset of the lymphocytosis and in other cases was lacking notwithstanding the lymphocytosis.

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6. Report on meeting of American Association for Cancer Research, 1913, in *Ztschr. f. Krebsforsch.*, 1913, xii, 441. Baeslack mentions also two cases of human cancer (sarcoma of upper jaw and carcinoma of uterus) in which during a period of retrogression there was an increase in lymphocytes. It may be also mentioned that Harlan Shoemaker (*New York Med. Jour.*, 1913, xlviii, 2-18) states that in the treatment of pellagra, after a first period of injections of colloidal copper, in which the polynuclears increase in the period directly following the injections, there is a later period during which the small mononuclear blood cells are increased, and still later the large mononuclear cells appear. This is an interesting observation. We believe, however, that we must distinguish between two phenomena, viz: 1. The temporary increase of polynuclear leukocytes following each injection of colloidal metal. Such a temporary reaction may still be present even at a later period, when the lymphocytes are already relatively and absolutely increased, and this increase in polynuclear leukocytes may superimpose itself on the lymphocytosis. 2. A later lymphocytosis, which in contradistinction to the increase in polynuclear leukocytes is not directly, but only indirectly, caused by the injections; it is a chronic condition lasting for a long period of time, after the injections have been omitted. It is not only produced through colloidal metals, but also through injections of casein and probably other substances causing a temporary increase in polynuclear leukocytes.

6. EFFECTS OF THE INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN ON THE TUMORS AND THEIR SURROUNDING TISSUES

We may divide the changes which we observed in two classes: (1) in those not directly representing healing processes, but processes more or less common to all tumors, and (2) changes representing a healing process, or the first stage of it, or a process, while not actually connected with healing, bringing some relief to the patient. A sharp line between these two kinds of effects cannot be drawn, and some might be just as appropriately classed with the one as with the other.

I. EFFECTS OF THE INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN ON THE TUMOR, NOT REPRESENTING HEALING PROCESSES

Besides the general effects which we described above, definite changes take place in the tumors and various tissues surrounding the tumors after the intravenous injections of colloidal copper and casein. *These changes might be characterized as a localized inflammation caused by substances introduced into the circulation at a place distant from the place of injections.* We have to deal with an experimentally produced inflammation. A localized effect is produced through an interference affecting the whole organism. The essential feature of the localized reaction is a hyperemia affecting the tumor and its neighborhood. It may not only affect the immediate neighborhood, but also extend somewhat further into the surrounding parts of the organism, and the extension is generally the greater, the more severe the reaction. For instance, if a lesion is situated at the lower lip and chin, the whole face may become swollen and the conjunctiva injected in the case of a severe reaction; and even the middle ear may show some effect. In open lesions the hyperemia may lead to small hemorrhages, which become noticeable in the form of hemorrhagic scabs over the ulcer or in a blood-stained secretion.

The hyperemia is followed by and is to a great extent the cause of the typical symptoms of inflammation, namely, swelling, redness, increased secretion and sensation of pain or allied sensations. The swelling following the injection can in some cases be seen soon after the injection, and can also be measured in favorable cases. Thus in a patient with a lesion affecting the humerus, the circumference of the arm would increase  $\frac{1}{2}$  to 1 inch after an injection. Even after the fourteenth casein injection such an increase could be observed. This swelling takes place sometimes during the period of rise of temperature; it occurs, therefore, before the maximum of temperature has been reached. But it may also be present somewhat later. Thus,

swelling of the neighboring lymph-glands was present four hours after injection and had subsided the following morning. The increase in hyperemia leads in the case of superficial lesions to redness of the surrounding tissue, and sometimes to a bluish purple coloration.

Increased secretion becomes noticeable in ulcerated tumors after the first few injections; for instance, as early as after the second injection. It may follow copper as well as casein injections. Sometimes a clear serous fluid is secreted, but at other times the secreted material may appear purulent or putrid. Infection of the ulcer by organisms is present in such cases. The swelling following the injections is in all probability due to the increased secretion as well as to hyperemia. If the increased transudate cannot be eliminated through an ulcerating surface, it might collect and cause swelling, as, for instance, in a cancerous lymph-gland, or in a lymph-gland not yet itself the seat of a metastasis, but situated in the neighborhood of a tumor.

The hyperemia and increased transudate causes also probably the pain or burning or itching sensation following injections in and around the tumor. These sensations may also radiate into a zone further removed from the tumor. For instance, in a case with a lesion in the right humerus, the pain was often felt not only in the diseased right, but also in the healthy left arm. These sensations are at their height just as the swelling before the maximum temperature has been reached. It may start three quarters of an hour or an hour after injection, and may have subsided within three hours. Local pain may be the most persistent symptom following the injections, more persistent than fever; such was the case, for instance, in the patient with a lesion of the humerus. Pain may be present after an injection of copper as well as of casein. If fever persists for several days after an injection, pain may also be felt for a few days after injection. Even with a slight fever, pain may be severe. Colloidal copper and casein produce essentially the same "inflammatory" reactions, only after casein the reactions were usually more severe; there was more pain, swelling and secretion. The relative intensity of the reactions following colloidal copper and casein varies in different cases. In some cases the reactions -- general as well as local -- are almost absent after colloidal copper, while they are marked after casein; in other cases they are present after colloidal copper, but stronger after casein.

There exists a definite relation between general and local reactions; in most cases both follow a parallel course. Usually a severe general reaction is accompanied by severe local reactions. For instance, in a certain case in which the general reaction following a certain number of injections was slight, the local reactions were also slight. Then there followed at a later injection a severe general reaction and the

local reaction also was much more marked than previously. In other cases the general reactions following injections of colloidal copper were entirely or almost lacking; in such cases the local reactions were also entirely or almost entirely absent. Furthermore, those preparations of casein which produce the most severe general reactions call forth equally marked local reactions. It may, however, occasionally occur that with relatively slight fever (99.8 F.) at one of the later injections, the local reactions (consisting, for example, in swelling of the face in a patient with a carcinoma of the lower lip) may be very severe. We may therefore conclude that the conditions determining the severity of the local and general reactions are the same; that there may, however, in some cases, in addition to these common conditions, exist some special conditions influencing separately either set of reactions.

We can more or less distinctly distinguish in most cases three periods as far as the character of the local reaction is concerned. In the first period all the inflammatory signs are most pronounced; increased redness and swelling around the tumor may be the first sign; a little later, at a fourth or fifth injection, increased serous discharge may become noticeable. The time relations in the appearance of these different symptoms differs, however, very much; also the duration of the first period, which extends usually from the first to somewhere between the fifth and tenth injection. Then the second period begins, characterized by a decrease in secretion; generally the secretion may become less and less during this period, and the ulcer becomes not infrequently almost dry; the swelling and the redness which existed previous to the treatment also often begins to subside. Quite marked in many cases is the diminution of pain during this stage, sometimes, however, a little earlier, during the first period. The second period is a period of reaction against the first period of more or less intense inflammation. Immediately following the injections there may, however, during the second period still be present local inflammatory reactions, varying in intensity in different cases and at different times in the same case. This second period is also the time when the more definite healing processes set in in cases in which such reactions can be observed. This second period gradually grades quite slowly into the third period of immunity against the local effects of the injections. Just as in the case of the general reactions, the immunity is usually not a complete one in the case of the local reactions; even toward the end of treatment severe local reactions may follow an injection; but gradually the severity becomes less. In some cases these reactions may be absent altogether, especially after a late injection of colloidal copper. Just as in the case of the general reactions, casein immunizes



also against the local effects of colloidal copper, while on the other hand injections of colloidal copper do not immunize against the effects of casein.

These periods, however, cannot be demarcated so sharply in all cases. There was, for instance, a case in which it required seventeen or eighteen injections for the diminution in secretion to become apparent, and this change in secretion was apparently the only difference between the different periods in this case. In another case local reactions appeared as late as the thirty-fourth injection of colloidal copper (throbbing pain around the tumor). In another case the first period extended over the first ten injections, and was therefore rather long.

In these three cases in which there was either no marked demarcation between the different periods, or the first period was of a long duration, the healing effect was also extended over a longer period than in the other cases. In these three cases (Nos. 1436, 1502, 1405), immunization against the effect of colloidal copper evidently took place to a less extent than in other cases.

Just as in the case of the general reactions, we have also in the case of the local reactions to take into consideration the fact that the doses of colloidal copper as well as of casein were in a number of cases gradually much increased as the injections progressed and that therefore a partial immunity may have been masked through the strong effects of large doses. The local reactions which we described were, naturally, mainly observed in the case of superficially situated tumors. But they occur also, as far as we can judge, in internal cancers and in lymph-glands with metastatic growths and internal organs in which metastases have formed.

Such lymph-glands also swell and become painful after injections of colloidal copper or casein during the first period. In one case of a primary carcinoma of the rectum with metastases in the liver, the first injection of 25 c.c. of a solution of casein was followed by pain in the liver region, evidently due to hyperemia in the liver surrounding the tumor. If a lymph-gland with metastatic nodules is connected through a fistula with the surface, the increased formation of transudate in the lymph-glands after injections may become apparent. In the second period we may also observe in the glands a diminution in the swelling and secretion. In a case of carcinoma of the esophagus there was less pain in swallowing after the ninth injection of colloidal copper. We may assume that this was due to a decrease in the swelling of the tumor with the onset of the second period. Similar phenomena were observed in a cancer of the breast. The breast as well as the neighboring lymph-glands became painful after injections of colloidal copper. After injections of casein there was also pain present in the axilla and in the

neighboring enlarged glands. Combined with severe general reactions following injections of casein, the pain could be present on days following the day of injection; in this case the fever also extended over a number of days. In the same patient the breast was swollen for one day after another injection of casein had been given. Here, too, we have to assume that increased hyperemia and perhaps increased transudate was the cause of these changes.

In a number of cases of ulcerating cancers we observed that after a relatively small number of injections the discharge from the ulcer, which had previously been putrid, changed its character and became very much less putrid. A possible explanation for this phenomenon is the bactericidal action of the serous transudate which, as we stated, is increased during the first period or perhaps at a somewhat later day; the succeeding increased dryness of the ulcer may also perhaps bring about this result.

While the local reactions may be concerned in the healing process, they are certainly not the only factor determining retrogressive changes in the tumors. The character of the lesion and the general condition of the patient also play a part. Thus we notice that the local reactions may still be present at a time when the healing processes have ceased. There were some other cases in which healing processes took place without marked local reactions or in which healing processes took place at a time when the local reactions had ceased. The opposite also occurs: there may be present marked local reactions without any healing processes being noticeable. On the other hand, we have stated already that in cases in which healing processes are noticeable, they usually set in with the second period. In one case especially a certain connection between local reaction and decrease in the size of the tumor was noticeable. In this case (No. 1405) the thirty-fourth injection of colloidal copper was followed by throbbing pains in the tumor, and in the course of the following few injections the size of the tumor diminished noticeably.

We may therefore conclude that while the local reactions following the injections are in some way directly or indirectly concerned in healing processes taking place in the tumor, these local reactions are not the only factors concerned, but other factors may be of equal or even greater importance for the healing process.

If we now inquire into the mechanism of these local reactions, it appears most probable that the presence of the tumor with the constant development of new vessels produces a special, labile, sensitive condition of the vessels in the tumor as well as in the surrounding tissues. In consequence stimuli, as, for instances, the presence of certain foreign substances, though unable to alter to any noticeable extent the

blood-vessels of normal tissues, have, in contact with these labile vessels, a similar action as the localized injection of certain very irritating substances in the case of normal tissues. In the production of pain the central nervous system is concerned. The radiation of the pain to a symmetrical part of the body (other arm) suggests an irradiation of stimulation within the central nervous system.

It is not probable that such localized reactions are restricted to real tumors, but it is probable that other localized lesions react in a similar manner. This is indicated by one of our cases in which local reactions took place at a time when in all probability the tumor was no longer present, if, indeed, at any time a real tumor had existed in this case.

## II. CHANGES IN TUMORS REPRESENTING HEALING PROCESSES

Among the local effects we have already mentioned, some changes induced by the injections which, inasmuch as they brought some relief to the patient, might in a wider sense be classed among the healing processes, as, for instance, decrease in pain, which was marked in a number of cases, decrease in secretion and in putrefaction, diminution in the swelling in the tissues surrounding the tumors or in the tumors themselves. In regard to the latter it is in certain cases difficult to distinguish between the decrease in size due to circulatory changes and a decrease in size due to the destruction of tumor cells, both processes occurring. It will be necessary to consider briefly the effect of the injections of colloidal copper and casein in a few selected cases.<sup>7</sup>

### A. NON-KERATINIZING, CYLINDRICAL-CELL CARCINOMAS OF THE SKIN

CASE 8 (No. 3614).—In part reported previously. Man, white, aged 34. During first period of the treatment observations were made by Dr. M. F. Engman and incorporated in our previous reports.<sup>8</sup> Multiple carcinoma of the skin on hand, face and neck. Numerous small cancerous ulcers, deeply infiltrating carcinomatous masses, destroying part of the nose, part of the skin in angle of eyes, some parts of lower lip. Lower lids of both eyes eroded. In tissues of left side of face were hard nodes of pea size. Lower lip greatly thickened, hard and everted. Skin rough and scaly. Three elevated plaques on the dorsal side of the hand. Disease started twelve years ago. Roentgen-ray treatment was tried without benefit. Thirty-six injections of colloidal copper; a large number of injections of casein extending over a period of more than four months. The injections of colloidal copper had no or only a very slight effect; our own interpretation of the action of colloidal copper is therefore less favorable than that of the first clinical observation of this case. There was perhaps a slight shrinking in the lesion of the nose; some crusts fell from the lesions, but similar changes had, as we found later, occasionally taken place spontaneously before the treatment was begun. The second injection of casein which had such marked general effects also led to marked local effects on the

7. For the sake of brevity, all other cases, comprising some of patients who were benefited, as well as the majority of those cases in which the results were slight or negative, are omitted.

8. Interstate Med. Jour., 1913, xx, No. 1.

tumor. Twenty-four hours after this injection many lesions appeared as if cauterized; after four days scabs fell from a number of lesions. The lesions of nose and upper lip healed almost entirely with the formation of scar tissue; some of the nodules of the lower lip became softer and disappeared. Some small lesions in the face disappeared; others remained unchanged. The following injections of casein had no marked effect. During the following six

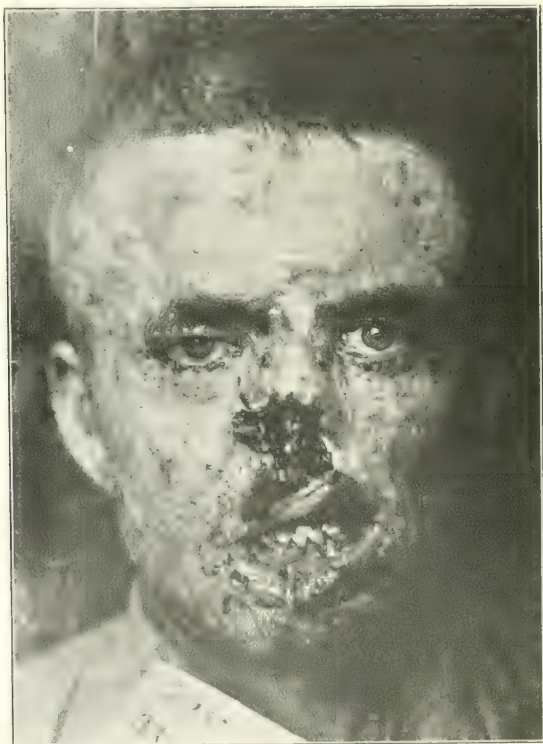


Fig. 1.—Photograph taken before any improvement was noted. (Case 8.)

weeks some of the lesions became softer. At a later period, when immunity had been established, one nodule around the face began to grow again. In a nodule examined microscopically towards the end of the treatment many mitoses were visible. The histogenesis of this tumor has been described elsewhere.<sup>9</sup>

9. Loeb and Sweek: *Jour. Med. Research*, 1914, xxviii, 235.

The photograph (Fig. 1) shows the condition of the patient at the beginning of the injections of colloidal copper. It shows the large carcinomatous ulcers around the nose and the upper lip. The small lesions in the face, the swelling and ulcers of the lower lip are brought out only indistinctly.

The photograph (Fig. 2) was taken three and one-half months after the beginning of the injections of casein. It shows the healing of the carcinomatous ulcers around the nose and the upper lip. At that time the swelling of the lower lip had become definitely smaller and the ulcerated masses were also somewhat smaller, but had not disappeared. Later this patient was again treated with Roentgen rays without marked benefit.



Fig. 2.—This photograph is not recent. The patient is in better condition than the photograph shows. (Case 8.)

CASE 9 (No. 1502).—Man, white, aged 57. Disease began as a small black speck below the eye twenty-five years ago; the lesion grew very slowly. Several plaster treatments led to temporary improvement only. Gradually the eye became involved. Nine years ago Roentgen-ray treatment was given, producing an improvement lasting one year. Eye extirpated. The ulcer grew more rapidly within last five years. There is now a crater-like ulcer involving socket of eye as well as the cheek below. Seventy-three injections of colloidal copper were given within a period of ninety-seven days. Twelve hundred c.c. was the largest single dose given. After the fifth injection an island of new skin began to appear; it increased later to finger-nail size. After seventeen or eighteen

injections the discharge diminished and was less putrid. The ulcerated surface looked healthier. Improvement continued. After the forty-fifth injection new skin extended from the margin of the ulcer deeply into the ulcerated area. The ulcerated area showed a raw surface with numerous patches of what appeared as granulations; some well-marked blood-vessels. During the period between the fiftieth and sixtieth injections the ulcer was again covered with some pus. From the fiftieth injection progress was slow, but the newly formed skin extended somewhat, showing, however, a macerated appearance. After the sixty-first injection there was less discharge, blood-vessels and skin extended somewhat. At the time of the sixty-third injection one Roentgen-ray exposure was given; two days later the general appearance of the ulcer was improved; some more new healthy skin appeared, a few days after the first and second exposures to Roentgen rays. Powder was applied over the ulcer; this led to improvement, diminishing the macerating action of the secretion. During nine days there was no treatment. After sixty-six injections the ulcer was almost entirely covered with skin. Some discharge was still present, originating in the eye-stump, at the seventy-third injection. The ulcer, with the exception of a small area along the side of the nose and at the outside corner of



Fig. 3.—This photograph was taken before treatment of any kind was employed. (Case 9.)

the lower edges of the former ulcer, was covered with new skin. At the end of the treatment most of the ulcer had healed over. There remained still a small ulcerated area one-half as large as a dime at the lower margin of the former ulcer and another one near the eye-stump. It is of interest to note that the progress continued, although the general reactions after the injections were usually slight. In this case we have much longer-continued effect than usual. The two Roentgen-ray exposures may have contributed to the improvement. Of interest also is the healing over, notwithstanding slight local and relatively slight general reactions.

The photograph (Fig. 3) shows the condition of the ulcer before treatment. At no place was the ulcer covered with new skin. Figure 4 shows the condition toward the end of April, after about sixty-three injections and immediately after a second Roentgen-ray exposure. The ulcer looks much cleaner and a bridge of newly formed skin traverses the ulcer.

Figure 5 shows the condition of the patient at the end of the treatment. The ulcerated area is almost entirely covered by skin; only two small places are still uncovered. This condition was still present three months after cessation of treatment. Here also immunity took place. Some small places did not heal over.





Fig. 4.—Patient shown in Figure 3 after about sixty-three injections and immediately after a second Roentgen-ray exposure. (Case 9.)





Fig. 5—Same patient as in figures 3 and 4, showing the condition at the end of the treatment and also three months afterward. (Case 1)



CASE 10 (No. 1436).—Woman, aged 69. In part previously reported. One year before the treatment was begun there was present on the bridge of the nose a small pearly growth with some ulceration in the center of the lesion. In the right ear involving the lower third and the auditory meatus, was an extensive destructive ulceration with considerable infiltration and swelling anterior to the mastoid process; the submaxillary lymph-glands were palpable. The lesion on the nose had at that time been present for one year; the lesion on the ear for three years. The patient was given Roentgen-ray treatment every other day until a reaction was produced on nose and ear. When the reaction had subsided, the nose was well and the lesion in the ear improved. She was soon given a second series of Roentgen-ray exposures without showing the same improvement as formerly. The tumor in the ear became larger and in the surrounding skin of the face and part of the scalp there developed eczematoid dermatitis. Staphylococcus vaccines and local antiseptic applications did not improve the dermatitis noticeably. The patient received in all seventy-eight Roentgen-ray treatments and when she entered the hospital in 1912 the tumor of the ear had grown double the size and the lesion on the nose had relapsed to its former condition. There was a discharging ulcerated patch beneath the ear and a tumor mass involving the seventh nerve, producing complete paralysis of the right side of the face. The patient received sixty-two injections of colloidal copper in seventy-eight days; usual dose 400 c.c., occasionally less; later nine injections of casein (2 to 8 c.c.). Corresponding with the onset of the second period healing set in. After the tenth injection of colloidal copper the ulcer appeared slightly shrunken, showing a thin dried scab. After the fourteenth injection the ulcerated area had several islands of new skin, also a line of new skin on the lower border extending upward over the ulcer. The skin around the ulcer appeared very much cleaner. After nineteenth injection the discharge had ceased, except from the auditory canal. The ulcer had healed from below upward, leaving a raw surface about as large as an adult middle finger nail. The skin around the ear was almost normal in appearance; only slight scales were noticeable, where before thick yellow crusted areas existed; clearing up of the eczematoid condition of the skin was simultaneous with healing. During the period from the nineteenth to the twenty-sixth injection the ulcer continued to shrink in size and a healthy crust formed over it. When the crust fell off, the ulcer beneath showed a healthy-looking skin; there existed no redness, edema or infiltrated margin around the ulcer. There was some discharge still from the meatus. After the twentieth injection the glands of the neck also were smaller. After the twenty-fifth injection dermatitis disappeared. Up to about the fortieth injection progress was still present, but slow. New formation of skin progressed, until at the end of the period only a small ulcer remained just below the auditory meatus, corresponding with the ulcerated area in the external auditory meatus. During the rest of the colloidal copper injections an ulcer of the size of a split pea remained under the external meatus. After the use of bismuth paste, the skin gradually extended toward the meatus, but no complete healing took place. The principal progress was therefore during the first twenty injections; it depended mainly on the contraction of the skin; but in the second place also on a healing over of new skin. There was some slight but continuous progress for more than two and one-half months. Then there occurred again a breaking down over a small area under the external auditory meatus. On the back of the left hand there was a large scab which would form, come off, and leave a raw, ulcerated surface beneath. After fifteen days' treatment no difference between the two hands was noticeable. The hand remained healed. The lesion on the nose had not disappeared, but was smaller, only a small ridge being left. The skin over the area formerly occupied by the growth under the ear showed some redness and appeared to be thinner than normal skin and had a tendency to form small white scales, which were easily removed. In this case the general

reactions after injections of colloidal copper were slight and cannot be held responsible for healing processes in the tumor.

The casein injections had no effect. During that period the ulcerative process even extended a little beneath and behind the ear for a few weeks and remained from then on stationary. Casein produced much stronger general

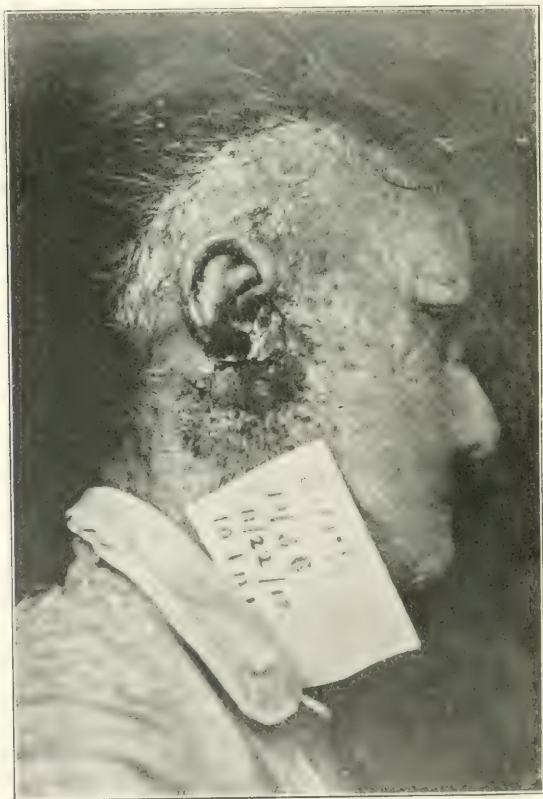


Fig. 6.—Photograph taken before any perceptible change had occurred. The dark spots outside of the ulcerated area are small ulcerated nodules. The date card covers a large mass of glands. This mass is easily palpable and slightly raised above the skin surface, but not sufficiently to show in a photograph. (Case 10.)

reactions than colloidal copper. Microscopic sections through the tumor at the time when it was beginning to progress a little, showed some strands of non-keratinizing carcinoma with a number of mitoses.



In this case there is a distinct immunization against the effect of colloidal copper noticeable. The main result was obtained in the period between the tenth and twentieth injections. From then on to the sixty-eighth injection the progress was much slower and during the period of casein injections the tumor even extended slightly. The healing remained incomplete. Later Roentgen rays were used without leading to a complete healing.

The first photograph (Fig. 6) was taken before any perceptible change had occurred. The dark spots outside of the ulcerated area represent small ulcerated nodules. The paper showing the date when the picture was taken covers a mass of swollen glands. The second photograph (Fig. 7), which was taken after the injections had been discontinued, shows that the large ulcerated area



Fig. 7.—Photograph of patient shown in Figure 6, taken after the injections were discontinued. The large ulcerated area is now covered by healthy skin. The mass in the neck is gone. The small dark patch in front of the external auditory meatus is a patch that refused to heal, owing to the irritation of the constant discharge from the ear. Examination May 2, 1913, showed that this place had healed and that there was no further progress of the growth. (Case 10.)

seen in the first picture is now covered by healthy skin. At this time also glands in the neck were no longer swollen. The small dark spot in front of the external auditory meatus refused to heal as a result of the discharge from the ear constantly irritating it. This picture also shows the improved condition of the skin around the tumor; the scaly appearance seen in the first picture has disappeared.

Among four cases of so-called basal-cell carcinoma, two were markedly improved, while one showed only a very slight improvement. In the latter case we had to deal with an anemic person with a deep ulcer. In the fourth case colloidal copper was also without noticeable effect, while one injection of casein with marked general effects led to a partial healing. In the latter case we have to deal with an indirect effect of casein. We see, therefore, even in cases representing the same type of cancer, marked variations in the results of the injections.

#### B. CASES OF SQUAMOUS-CELL CARCINOMA

CASE 11 (No. 1455).—Man, white, aged 46. Three years prior to admission the patient had a sore on the lower lip; about two years later the sore began to spread. Treatment by paste made the condition worse. Now ulcerated area on right side of lower lip beginning at mucocutaneous border; hard everted edges; at lower half edges hang over to extent of 1 cm. Mass hard. Through mucous membrane hard nodules can be felt. Ulcer about  $1\frac{1}{2}$  inches in diameter. An enlarged lymph-node under chin. Forty-six injections of colloidal copper (up to 500 c.c.) were given. Following the second injection of colloidal copper there was less pain. Following the seventh injection the edges of the ulcer softened; the ulcer was somewhat smaller. Following the tenth injection it was distinctly smaller; skin began to grow over the ulcer. These changes took place notwithstanding very slight general reactions. Up to the fourteenth injection the ulcer became still smaller. Following the seventeenth injection the nodule under the chin disappeared. After the twentieth injection the mass on the lip became still smaller, softer and could be folded. From then on only very slight changes occurred up to the thirty-first injection. The lip became movable; a little skin grew over the edge of the ulcer. During the casein injections there was no definite progress. Histological character of pieces taken out at an early and a late stage of the treatment was about the same. There was evidently in this case immunity produced after the first twenty injections of colloidal copper.

CASE 12 (No. 1476).—Man, aged 59. Carcinoma of cheek of sixteen years' duration. Cauliflower-like ulcerated carcinoma of left cheek of size of a 5-cent piece covered by yellowish-red scab, raised about 1 cm. above level of cheek. This growth was the center of an indurated area about two inches in diameter which was covered by reddened skin, extending down to but not involving the mucous membrane of the cheek. Could be distinctly felt on inside of mouth. Case declared inoperable on account of size of surrounding indurated area. Thirty-five injections of colloidal copper, eighteen injections of casein. From sixth to fourteenth injection the indurated mass around the tumor began to diminish in size; diminution continued up to the sixteenth injection. From then on there was a stationary condition. From the fourteenth to the seventeenth injection pain in the tumor disappeared. Central tumor not smaller, but easily movable. Casein without effect. Microscopically no change at beginning and end of treatment. Immunity after about fourteen injections; very slight general reactions in this case. After the series of injections the tumor could be apparently easily completely removed through operation.

CASE 13 (No. 1442).—Carcinoma of right cheek affecting lower jaw, extending to angle of jaw and into lower lip. In the lower part of swelling there is a protruding fungus-like ulcerated mass about three-fourths inch in diameter. Thirty-six injections of colloidal copper and twenty-seven injections of casein were given. Following the fourth injection of copper the external mass was somewhat reduced in size; following the tenth injection the tumor masses were smaller; soreness disappeared; patient opened mouth better. Fungus-like

outgrowth on outside of cheek had shriveled considerably and discharges less. After the seventeenth injection some shrinking in oral cavity; mass in mouth became movable; could open mouth much better; external prominence had shrunk. After end of copper treatment (Jan. 15, 1913) no copper found in section of tumor taken out. Four days after first injection of casein which produced marked general reactions, tumor noticeably smaller. Mass within mouth had diminished in size. The mass in the mouth which had been reddish before became grayish-white and appeared necrotic. Part of necrotic material was expectorated. Outer excrescence dried up. No change from further injections. Immunity began after ten injections of colloidal copper and was almost complete after twenty injections. There was also some immunity against general effects of colloidal copper. There was a necrotizing effect of first casein injection on the tumor.

CASE 14 (No. 1405).—Man, aged 74. Formerly reported; irregular ovoid mass apparently attached to periosteum over antrum. Continuous with this mass there is, in the buccal tissue, another swelling that appears on the mucous surface of the cheek as a leukoplakic area, raised about 2 mm. above the surrounding healthy mucosa. On gum and hard palate several small yellow nodules; sixty-two injections of colloidal copper (from 150 to 400 c.c.) From the seventh injection on, less pain in the face. After twelfth injection could open mouth and eat. From the twenty-fourth to the twenty-eighth injection, there were still less pain and further improvement in the general condition. No change in external mass of leukoplakia. During the period from the twenty-eighth to the thirty-sixth injections the external mass diminished steadily in size. At the time of the thirty-second injection the swelling was noticeably smaller. Following the thirty-fourth injection there was marked local reaction and subsequently swelling became markedly smaller and had disappeared after the thirty-sixth injection. Up to the forty-sixth injection the tissue continued to become softer and more movable, and the mass fixed on the periosteum could no longer be felt. Movements of the mouth were no longer restricted. Leukoplakic area and yellow spots persisted. No further changes took place. Up to the end of treatment microscopic examination of leukoplakic area showed much thickened epithelium with relatively small processes into the deeper tissue and some round-cell infiltration in the connective tissue below. There was a gain in weight during the period of injections. In this case there was no immunity against general reactions, and the main retrogressive change on tumor took place between the thirtieth and forty-sixth injections.

If we summarize briefly the effect of the injections of colloidal copper in cases of squamous-cell carcinoma (including some cases in which the microscopical examination could not be carried out), we find definite retrogressive changes in Cases 1404, 1442 and 1455, changes which could not be explained merely through alteration in blood and lymph circulation. In one case, T., in which the progress had been rapid before the treatment had been begun, at least a standstill followed the injections. In Cases 1499 and 1405 the diminution in the swelling was marked, but it is difficult to determine how much of it was due to alteration in the circulation through the tumor and surrounding tissues as the result of the injections. Such circulatory changes led also to a marked diminution in size in the Cases 1439 and 1298; in Case 1476 they were marked, but concerned the tissues surrounding the tumor proper; they rendered the removal of the tumor through operation possible. In the following cases there was only a

very slight or no retrogressive effect visible, or it was of such a kind that later experience made it doubtful whether the effect was due to the injections or to spontaneous changes: 1430, 1132, 1453, 1458, 1441, 1420, 1504, 1412, 1454. There were, however, some slight effects present in some of these cases; thus Patient 1412 could move the eyelids, close the eye much better and could open his mouth much wider than before. Similar improvement was noted in Patient 1405. There was a decided diminution in pain in the following cases: 1455, 1405, 1458, 1404, 1439, 1412 and 1454. Putrid discharge was diminished in Cases 1458 and 1454. As to the effects of casein, we noticed in a manner similar to Cases 3614 and 1442, and to some extent in Case 1504, that an injection which has a very marked general effect on the patient may cause a part of the tumor to become necrotic, and later on to be cast off; the effect of such an injection does, however, merely affect a certain part and not the whole of the tumor. Otherwise it is doubtful whether injections of casein have any effect on the tumors, although they have more marked general and local inflammatory effects than injections of colloidal copper. There was perhaps a slight effect of casein present in Case 1420, in which the injections of casein preceded those of colloidal copper, and also in Case 1298. Of great interest is the fact that most of the healing changes, or changes leading to the relief of the patient, took place in the course of the first sixteen or twenty injections. Case 1405 was an exception in this respect. The principal changes took place, therefore, in the second period, or in the time directly following it.

In the following case the diagnosis of sarcoma could not be established with certainty:

CASE 15.—M., white girl, aged 16. Mother and grandmother of patient had been operated on for cancer. Swelling in right upper arm at junction of upper and middle third, about size of silver dollar, very sensitive to touch; pain especially on motion. Pain was noticed first about three months previously. Diagnosis of sarcoma was made by a well-known surgeon and immediate amputation of arm recommended. Roentgen-ray picture was taken before the injection was begun; she was kept under observation for twelve days; at the end of this period another Roentgen-ray picture showed that the growth had progressed. Circumference of arm at point of disease was 11 inches at the beginning and 11½ inches at the end of the period of twelve days. Six injections of colloidal copper (100 to 400 c.c.) and forty-six injections of casein in 117 days (from 15 to 25 c.c.) were given. After three injections of copper, five days after the beginning of the treatment, the circumference of the diseased arm had decreased ¼ inch. Directly following the first injections of casein there was an increase in the size of the diseased area, which was followed by a decrease. A Roentgen-ray picture five and one-half weeks after the beginning of the treatment (after about twelve injections of casein) showed a standstill in the disease; another Roentgen-ray picture was taken three or four weeks later which showed a new deposit of lime salts in the diseased part; this calcification progressed during the next few weeks; after the thirty-seventh injection about one-third of the area was infiltrated with lime salts. From then

on no or only very slight progress was made till the end of the injection. About three months after the last injection the diseased area was opened through operation. A cavity and necrotic bone were found; microscopically, connective tissue, partly rich in cells, was seen, and some necrotic bone invaded by connective tissue. In this case the diagnosis of sarcoma cannot be made with certainty.

In accordance with our previous observations, we found in a case of carcinoma of the breast that a single general reaction of great intensity following an injection of casein may lead to a partial destruction of tumor tissue. Injections of colloidal copper, in cases of cancer of the breast, led only to some diminution in the size of lymph-glands approximately coincident with the beginning of the second period. We treated three cases of carcinoma of the uterus; two of these were very advanced in very cachectic patients; one was less advanced in a relatively robust woman.

CASE 16 (No. 369).—Negro, woman, aged 30. Examinations by Dr. F. J. Taussig. Patient hysterectomized for carcinoma of uterus about four years preceding the injections. Recurrence. A mass the size of an orange, irregular in outline, palpable, was found in the right iliac region; a similar mass about one-half the size of an orange in the mid-pelvic region; about nineteen injections of colloidal copper (150 to 400 c.c.) were given.

After two days tumor on right side the same; in center a little smaller. After fifteen days right tumor smaller, tumor in center had continued to shrink and had become flatter. After twenty-one days pain had disappeared; there was very slight sensitiveness on deep pressure. No change in consistency. The right tumor continued to get smaller up to the end of treatment; the gland in the center was at that time hardly palpable. After discontinuation of treatment the disease began again to progress. There was no doubt in this case concerning the beneficial effect of the injections, which produced a considerable reduction in the size of the tumor and diminution in pain.

In a non-cachectic patient colloidal copper improved the condition of the patient markedly, causing a noticeable reduction in the size of the tumor. In this as well as in the one of the two cachectic patients, colloidal copper diminished pain markedly, while in the third cachectic patient neither tumor nor pain was influenced. We may furthermore conclude that the injections are capable of influencing, also, tumors other than those of the skin or external mucous membranes.

Some decrease in the size of the tumors was observed in a case of cancer of the thyroid. We leave it open in this case as to how much of this decrease was caused through circulatory changes.

## 7. CONCLUSIONS

### I. SUMMARY OF EFFECTS OF COLLOIDAL COPPER AND CASEIN ON THE HEALING PROCESSES

1. Intravenous injections of colloidal copper have a definite effect in a certain number of tumors, while in the case of others they are without any noticeable effect. It is at present only to a limited extent possible to analyze the factors responsible for this variability in the



results. In a preliminary manner we may conclude that: A. The effect of the injections is not limited to a special kind of cancer. Definite results have been obtained in the smaller basal-cell as well as in squamous-cell carcinoma and in carcinoma of the uterus. The most marked results were, however, obtained with the least virulent, most chronic cases, namely, the smaller basal-cell carcinoma. B. Those patients in whom definite results were obtained were relatively vigorous persons. In cachectic patients and in those with internal metastases, no results were obtained, and in some cases it was observed that following an intermittent disease which weakened the patient very much, injections which had previously had some effect, became indifferent. C. While these factors seem to be of importance, other variable factors seems to play a part, and it is therefore impossible to predict in a given case whether or not a definite result will be obtained.

2. While in some tumors the measurable reduction in size, the shrinking of the ulcerated area, leaves no doubt about the definite effect of the injections on the tumor, there are a number of cases in which a noticeable shrinking of the tumor takes place, but in which the character of the tumors and the rapid effect of the injections suggest that the diminution in size is mainly due to an effect on the circulatory conditions in the tumor, as for instance, in Case 1439. In other cases, as, for instance, 1405 and 1513 (carcinoma of the thyroid), it is doubtful how much of the change observed is due to the circulatory changes and how much to an actual decrease in the quantity of tumor tissue. In one formerly rapidly progressing case the growth came to a standstill during the period of injections. In certain cases the injections do not influence to any noticeable extent the tumor itself, but they cause a marked diminution in the swelling of the surrounding tissues (especially in Case 1476). Through this sharp demarcation of the tumor proper a formerly inoperable tumor may become converted into an operable tumor. There was also an effect noticeable in the glands affected by metastases; a diminution in size was observed in a number of cases; again, changes in the circulatory condition may entirely or partially be the cause of this. In a number of cases a marked diminution in the pain, and, in some cases, in the quantity of the putrid discharge, followed the injections. In a considerable number of cases neither objective nor subjective improvement could be obtained.

3. In most cases the improvement began approximately with the onset of the second period (see general description of local reaction). In almost all cases the improvement after a temporary period of progress came to a standstill. The duration of the period of progress in healing varied considerably in different cases. We noticed a similar gradual decrease in the effects of the injections in the cases of the



general reactions and local reactions in the region surrounding the tumor. There was in some cases a parallelism noticeable in the curves indicating the gradual decrease in the reactions of a general character and those affecting the tumor directly. We may interpret this decrease in the effect of the injections on the tumors in two ways: A. Certain parts of the tumor or certain processes in the tumor are much more accessible to the actions of colloidal copper than others. After they have been influenced, other parts or other processes remain inaccessible to the effect of colloidal copper. B. An immunity is gradually obtained, not only against the general reactions, but also against those local reactions which induce healing processes. Inasmuch as we have proved the existence of such an immunity in the case of animal cancers, and have shown it to be of double origin, it becomes very probable that an analogous immunity is also produced in human cases. In addition, the first-named factor may play a certain part. Thus, it comes about that even in the apparently most favorable cases the healing remains incomplete and later even the progress of the carcinomatous growth may be observed. A similar immunity is produced against the general reactions following the injections of colloidal copper.

4. Microscopical examinations of pieces of tumor excised during different periods of the treatment do not indicate a direct destruction of the tumor. This is not conclusive evidence, however, against the occurrence of such a process, inasmuch as one of us has shown previously that also in definitely retrogressing animal tumors mitoses may still be found in tumor cells.<sup>10</sup>

5. While intravenous injections of colloidal copper have a definite effect, causing a partial retrogression in a certain number of cases, ordinary injections of casein preparations were even without effect or were followed by so slight effects that the distinct efficacy which can to a limited extent be ascribed to colloidal copper cannot be attributed to casein. In two cases, however, there were perhaps slight effects visible (1420 and 1298); these were cases in which the injections of casein had not been preceded by a larger number of injections of colloidal copper. We may interpret this lack of efficacy of casein in either of the following two ways: (A) Casein is actually without effect in human cancer, despite the fact that it is efficient, although to a less extent than colloidal copper, in animal tumors. Or (b) the lack of efficiency is only apparent, caused by the fact that in almost all our cases the injections of casein were preceded by injections of colloidal copper, and that through the preceding injections of colloidal copper an immunity had been produced against the action of casein as far as

10. Loeb: *Virchow's Arch. f. path. Anat.*, 1902, clxvii, 187; *ibid.*, 1903, clxxii, 363.

its direct effect on the tumors is concerned. Then it would be necessary to conclude that such an immunity against the direct effects of casein on the tumor could thus be produced, while, as we saw above, preceding injections of colloidal copper are not able to produce an immunity against the effects of casein as far as its general and certain inflammatory local reactions are concerned.

6. While a definite decision between these alternatives cannot be arrived at at present, we may definitely conclude that there is no thorough-going parallelism between the strength of local inflammatory reactions or the severity of the general reactions following the injections of a certain substance and its direct effect on the tumor.

7. In case injections of casein have an unusually marked general effect, causing high fever, extending over several days, combined with other severe symptoms, they may cause a partial destruction of the tumor within the next few days following the injection. This partial destruction may result in a localized process of healing. In no case was more than a partial effect accomplished by these means. This effect is in all probability not to be considered as a specific casein reaction, but it may be that any other substance causing very marked general reactions would have similar effects on the tumors.

8. As far as the general and local inflammatory reactions following the injections are concerned, our investigations have shown, in accordance with what we assumed from the beginning, that the local reactions around the tumor following the intravenous injections of various substances are in no way specific.

9. Some other investigators have made observations which support the conclusions that intravenous injections of colloidal copper, or of related substances, have a definite effect on a certain number of tumors, while others, the majority, are left uninfluenced. Thus Dr. M. J. Gelpi, in the Department of Gynecology at Tulane University, New Orleans, injected several patients with a solution of colloidal copper hydrate.<sup>11</sup> Among them he observed a case of carcinomatous ulcer of the cheek which healed entirely over as the result of the injections; an indurated area, however, remained unchanged.

Furthermore, there have also appeared reports by various observers in different countries, some on cases which show undoubtedly that injections of various colloidal metals have a definite, though, from a practical point of view, only partial, effect on a certain number of tumors. On the majority of tumors no or only a very slight effect could be determined.

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11. A preparation of Mulford & Co., Philadelphia. We tested the same preparation in mouse tumors. See our communication in *Jour. Exper. Med.*, 1914, xx, No. 5. The case will be reported by Dr. Gelpi. In that case also a recurrence may have taken place later.

10. We have found some evidence supporting the conclusion that human and animal tumors are affected fundamentally in a similar manner by certain substances introduced into the general circulation. Colloidal copper has on cancer in animals a definite though by no means very strong effect. It has also an effect on a certain number of human cancers. We proved the existence of a process of immunization in the case of animal tumors after repeated injections of various substances and we analyzed its mechanism. While a proof of this immunity cannot be given in the case of human tumors with the same definiteness as in the case of animal tumors, its existence can at least be made very probable, a conclusion of theoretical as well as of practical importance.

## II. SUMMARY OF EFFECTS OF INJECTIONS OF COLLOIDAL COPPER AND CASEIN NOT RELATING DIRECTLY TO HEALING PROCESSES

11. Colloidal copper, and probably also other colloidal metals, in contact with the walls of the veins cause pathological changes. Solutions of casein do so only exceptionally. The intensity of these changes depends on all those conditions which favor or inhibit an intimate contact between the colloidal particles and the endothelium of the blood vessels. The colloidal particles of metals produce, probably through injury of the endothelial cells, a greater permeability of the vessel-wall for the fluid constituents of the blood, and cause sometimes a dilatation of the vasa vasorum, leading to inflammation in the neighborhood of the vessels.

12. Immunity against the effects of colloidal copper produced through repeated injections of the solution is one of the factors determining the rise of temperature following the injection. The immunity produced against the effects of colloidal copper on the temperature is not specific; it can be produced through preliminary injections not only of colloidal copper, but also of casein.

13. Under similar conditions very small doses of casein cause a greater rise in temperature than colloidal copper, and the fever curve is steeper after casein. In individual cases the rapidity with which the fever disappears varies very much; it is probable that the duration of fever depends at least partly on the time during which unchanged or only slightly changed casein circulates in the blood, while in later periods, when the organism is in a position to split the casein more rapidly, the temperature returns more rapidly to the normal point.

14. Injections of casein are followed by an immunity against the general effects of casein; this immunity gradually increases with the progress of injections. It appears as early as after the first three or four injections; on the whole, three periods can be distinguished in its

development. Immunity may be established in strong as well as in weak persons, in whom there may be metastases present at the time the injections were given. Intervals of ten or nineteen days may elapse between two succeeding injections of casein without the appearance of definite symptoms of anaphylaxis. While preliminary injections of casein protect against the general effects of colloidal copper, preliminary injections of colloidal copper do not diminish markedly the effects following the injections of casein. There exists a certain parallelism in the curves of immunization following injections of casein and of colloidal copper.

15. Intravenous injections of colloidal copper or casein, if given through a considerable period of time, cause a relative increase in (especially small) lymphocytes and a corresponding decrease in polynuclear neutrophil leukocytes. This change extends over a long period of time and may still be present many months after injections have been suspended.

16. Intravenous injections of colloidal copper and casein cause in and around the tumors changes which might be characterized as a localized experimentally-produced inflammation called forth at a place distinct from the place of injection through substances introduced into the general circulation. Colloidal copper and casein produce essentially the same "inflammatory" reaction, only after casein the reactions are usually more severe.

17. We can in most cases distinguish three periods as far as the character and intensity of the local reaction is concerned. In the first period all the inflammatory signs are most pronounced. The second period is characterized by a marked decrease in inflammatory reactions. In cases in which the injections lead to an improvement in the conditions of the patients, the healing changes usually set in with the second period; the second period represents a reaction against the first period. The third period is the period of more or less marked immunity against the effects of the injections. Just as in the case of the general reactions, so also in the case of the local reactions, an immunity usually becomes established, which in this case likewise is usually not complete. In a similar manner as in the case of the general reactions, casein immunizes also against the local effects of colloidal copper, while, on the other hand, injections of colloidal copper do not immunize against the effects of casein.

While a certain connection between the local reactions and the healing processes seems to exist, the parallelism is not a complete one, probably owing to the interference of other variable factors.

It is possible — and we regard this as entirely tentative — that the reaction against the acute inflammatory changes of the first period, a

reaction which characterizes the second period and which leads to a diminution in the size of the tumor and its neighborhood mainly through circulatory changes, constitute the essential effect of the injections of colloidal copper, and that in some special cases this change is followed by further healing processes, either by a more marked shrinking of the tumor or by a healing over of the carcinomatous ulcer. Whether an actual destruction of tumor tissue takes place directly or indirectly as the result of the injections, can neither be positively asserted nor denied at present.

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## RAT-BITE FEVER\*

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### 1. INTRODUCTION

In 1907 my attention was first called by Dr. E. Libman to an observation which he had made on a patient who had been bitten by a rat, and who, two weeks later, had developed an irregular and intermittent fever, accompanied by a diffuse erythema, and terminating in recovery without sequelae. Though no distinct scientific data were taken at the time, the unusual character of the symptoms attracted his attention. Soon afterward, two other somewhat similar occurrences were remarked by medical associates, but no opportunity was afforded for personal observation of these cases.

The appearance of an article by Horder<sup>1</sup> in 1910 describing three cases of irregular fever following the bite of a rat, and the almost simultaneous occurrence in the wards of Mt. Sinai Hospital of an undoubted instance of similar nature, afforded the opportunity of making a complete study and examination of all the data in this case and a careful scrutiny of the literature of the various countries in an attempt to discover the previous recognition of the symptom-complex and to collate all the information obtainable relative to the subject. It soon became evident that a distinct clinical picture following the bite of a rat in a human being had been recognized in the older and the more recent Japanese literature, as well as in the older American literature, and that there were sporadic references to similar occurrences in the medical archives of at least three nations of Europe.

Since 1910 there has been an increasing number of cases reported, particularly in the British literature, while the recent records of our own country, except for the isolated report of Proescher<sup>2</sup> in 1913, remain devoid of a single instance. On the suggestion of Dr. Libman, and with the desire to give further recognition to a disease both interesting and important and well worthy of a closer scrutiny, the following case is reported, together with a careful review of the literature of all countries.

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\* From the Pathological Laboratory, Mt. Sinai Hospital.

1. Horder: *Quart. Jour. Med.*, 1910, iii, 121.

2. Proescher: *Berl. klin. Wchnschr.*, 1912, xlix, 841; *Internat. Clin.*, iv, series 21, p. 77.



## II. CASE HISTORY

*Patient.*—A Russian boy, aged 15, was admitted to the first medical service of Mt. Sinai Hospital (service of Dr. J. Rudisch) Dec. 17, 1910, giving the following history: About two and a half weeks prior to admission the patient was bitten on the scalp by a rat. After the bite he complained of nothing but slight pain. The wound seemed to heal without attention. Two weeks later, on account of pain and swelling about the healing wound, he consulted a physician. The latter found an edema and induration on the scalp over an area about the size of a bean. There were some enlarged cervical lymph-nodes on the same side, which had been there for a week, according to the statement of the patient. The physician made a crucial incision over the site of the bite and swabbed the parts with potassium permanganate. Fever developed three days later. The glands in the neck increased in size and the eye-lids became swollen. There was a purplish discoloration of the face and right eye. Vomiting occurred on several occasions during the previous week. When admitted to the hospital the patient was sent to the isolation house for supposed erysipelas originating in the wound.

*Physical Examination.*—December 18. Patient well nourished; does not look seriously ill. No cyanosis or dyspnea. Temperature, 102.2 F.; pulse, 100.

*Skin:* Over the entire right cheek, right side of the forehead, right side of the neck, right ear, and over a small area behind the right ear there is a diffuse erythema of which the margin is only moderately well defined. Over the area on the neck are a few large blebs and superficial excoriations (due to the use of local applications).

*Nodes:* Cervical, axillary and inguinal nodes on both sides are slightly enlarged.

*Scalp:* Over the right side behind the angle of the jaw there is a group of enlarged lymph-nodes;  $3\frac{1}{2}$  inches above the right eye is an open wound discharging a small amount of serum. The wound is surrounded by a slight induration and some edema.

*Heart and Lungs:* Negative.

*Liver:* Extends to the free border of the ribs. Upper border of flatness in the fifth intercostal space.

*Spleen:* Edge distinctly felt one finger below free border; hard and round. Extremities and reflexes normal.

*Course.*—December 19. Edema and erythema have spread to the other side of the face and eyelids. The temperature has become normal.

December 20. General condition good. Temperature normal. No signs of progress of erythema. Original wound is almost clean.

December 22. Patient discharged, well, the induration about the wound and the erythema having disappeared.

*Abstract of Clinical Data.*—Temperature: See chart. Pulse: Ranged from 70 to 90 or 100, then 68 to 72. Respiration: Normal. Amounts of Urine: Normal. December 18. Clear; acid; 1.030; trace of albumin; no acetone or indican present; moderate number of hyaline and granular casts and some leukocytes. December 20.—Trace of albumin and many hyaline and granular casts and moderate number of leukocytes and occasional erythrocytes. December 22. Faint trace of albumin; few leukocytes; no casts.

*Treatment.*—Patient treated symptomatically as an erysipelas case.

*Summary.*—It will be noted that the patient having been bitten by a rat, the wound promptly healed. After an incubation period of two weeks, edema and erythema occurred about the healed wound. Incision and cauterization of the parts were ineffectual in preventing spreading inflammation. Regional lymph-nodes were early enlarged. Fever appeared shortly after the inflam-

matory signs. After a course of five days, characterized by fever and local inflammation, erythema, adenitis and mild nephritis, the symptoms spontaneously resolved.

The patient was readmitted to the first surgical service of the hospital Dec. 29, 1910, and was transferred to the first medical service Jan. 11, 1911.

*Surgical History.*—The patient stated that two days before admission (or eight days after resolution of previous symptoms) a small mass developed behind the lobe of the right ear. It was painful and tender. The swelling had steadily increased, and the patient said he was forced to keep his head bent to the right shoulder so as to relieve the pain. He felt feverish and somewhat chilly. He was not hoarse, but swallowing was painful.

*Physical Examination.*—This revealed no new symptoms. The wound was healed; there was no erythema. The cervical nodes were markedly swollen; other lymph-nodes not enlarged. Lungs and heart negative. Liver not palpable; spleen palpable two fingers below the free border of the ribs, firm and round. Temperature, 102 F.; pulse, 100. The urine showed a severe nephritis to be present.

December 29: Aspiration of nodes with negative results.

December 31: Temperature normal.

(The defervescence marks the end of a second paroxysm characterized by swelling of nodes, fever, chilliness, dysphagia and pain in the wound).

January 3: Urine examination shows a faint trace of albumin and a few epithelial cells and leukocytes.

January 8: Urine examination negative.

January 9: The regional nodes are slightly larger. There is slight tenderness of the sublingual lymph-nodes. Axillary nodes not palpable. During the preceding nine days the temperature has remained normal and the patient has been comfortable.

January 11: Temperature shows another rise, reaching 101.6 F. There is no change in the wound. Behind the ear, extending backward to the trapezius muscle and downward to the anterior border of the sternocleidomastoid muscle is an erythema which is, for the most part, patchy. In places it is confluent, pink in color, slightly elevated, resembling urticarial erythema. A group of enlarged lymph-nodes exists behind the angle of the jaw, extending to the lobe of the ear; the mass is the size of a plum, the nodes are quite tender. There is one small, tender lymph-node in the right axilla. Left axillary nodes just palpable. The spleen is palpable  $1\frac{1}{2}$  fingers below the free border of the ribs; the edge is round and firm. The liver is palpable two fingers below the free border of the ribs.

Blood-Counts: January 2.

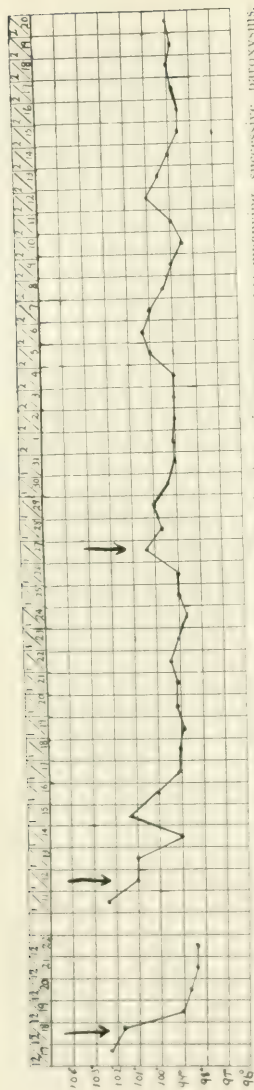
Erythrocytes .....	5,000,000
Leukocytes .....	16,000
Polymorphonuclear leukocytes .....	75 per cent.
Lymphocytes .....	21 per cent.
Eosinophils .....	4 per cent.

January 9.

Leukocytes .....	11,000
Lymphocytes .....	20 per cent.
Polymorphonuclear leukocytes .....	80 per cent.

The patient was transferred to the medical service.

*Second Medical History.*—Examination January 12. The patient is somewhat apathetic. In the right temporal region is the original rat-bite; extending from one-half inch from the median line backward as far as the coronal suture there is an area of slight edema which on pressure is not tender, and which extends down over the posterior half of the right side of face. At the angle of the jaw there is a mass of lymph-nodes about the size of a lemon;



Temperature chart of author's case of rat-bite fever. Arrows mark rises of temperature accompanying successive paroxysms. During the period between December 22 and January 11, the patient was not under observation.

somewhat tender, not attached to the skin; the nodes are somewhat matted together in this region. The submaxillary nodes are enlarged but not tender. There is fullness in the right supraclavicular fossa, and also in outer half of right pectoralis major muscle, this area being tender on deep palpation. In the right axilla the nodes are matted together. Posterior cervical nodes are somewhat enlarged; lymph-nodes elsewhere in body slightly increased in size. There are no changes of any importance in the mouth or throat.

Liver: Palpable two fingers below free border; edge sharp and smooth.

Spleen: Palpable two fingers below free border; edge smooth and hard.

Temperature, 101 F.; pulse, 96.

Urine: Very faint trace of albumin; otherwise negative.

January 13. Spleen broad and palpable one finger below free border. Nodes are larger and more tender.

#### Blood-Count:

Erythrocytes	4,800,000
Leukocytes	9,000
Polymorphonuclear leukocytes	.62 per cent.
Small lymphocytes	.17 per cent.
Large lymphocytes	.17 per cent.
Large mononuclears	.2 per cent.
Eosinophils	.2 per cent.

January 17. During the last four days the temperature has been defervescing and the erythema has almost entirely disappeared. Nodes in the submaxillary region are growing progressively larger; otherwise lesions the same as before.

[This paroxysm (the third) occurred after a free interval of ten days. It was characterized by early regional and general lymph adenitis, fever, chilliness, local erythema, enlargement of the spleen and nephritis.]

January 23. Urine shows a very faint trace of albumin; no casts.

February 15. Since the last note the general condition has remained good; patient is up and about. Lymph-nodes still enlarged, not tender; diminishing in size. Erythema disappeared shortly after the end of the last paroxysm.

February 17. Notes on discharge: No edema; no erythema present. Incision (made in removal of lymph-node) behind the ramus of the jaw is healed primarily. Behind the ramus of the jaw there is a lymph-node the size of an almond which is rather firm and quite tender. Surrounding this node there are a number of firm, tender nodes, lobular in form, varying in size from a pea to a hazelnut. Down to the supraclavicular region there is present a large number of lymph-nodes of the same type as those described before, about the size of a pea.

The glands are not matted together, but some of them are connected by strands, apparently of fibrous tissue. Just below the angle of the jaw on the left side there is present a lymph-node about two-thirds the size of an almond, and fairly soft in consistency. In the supraclavicular region on the left side there are no lymph-nodes.

In the left axilla no lymph-nodes are palpable.

In the right axilla two lymph-nodes are felt agglutinated together, fairly soft in consistency, each about the size of a small pea.

In both inguinal regions there are small, fairly soft lymph-nodes about the size of split peas.

In the right recumbent position, splenic dullness begins in the sixth space in the axillary line. Spleen, on deep inspiration, comes down two fingers' breadth below free border. Edge is sharp and hard.

Liver dullness begins in the fourth space in the mammillary line, but is not enlarged downwards.

Lungs and heart are negative. Patient in good condition.

Temperature: For the temperature January 11 to 17, see chart. After January 18 the temperature was practically normal, except for an occasional rise to 100 F.

Treatment.—Purely symptomatic.

(This patient was seen by Dr. Libman a number of times up to March 15, 1911. There had been no further acute attack; the lymph-nodes on the angle of the right jaw were still moderately enlarged and the spleen was still palpable).

Pathological Data.—A blood-culture was made by Dr. Daniel Poll Dec. 17, 1910, when the temperature was 102. Fifteen cubic centimeters of blood were used. The blood was distributed in plain bouillon, glucose-bouillon, agar and glucose-agar. It was incubated partly aerobically and partly anaerobically. No growth in any of the mediums was observed (time of observation six days).

A second blood-culture was made Jan. 9, 1911, when the nodes were enlarging. Fifteen cubic centimeters of blood were used. This was inoculated in ordinary bouillon, ordinary agar, and glucose agar, and grown aerobically, with negative result.

Blood was also inoculated into deep tubes of glucose-agar (according to the Veillon method) and observed for two weeks. Results were entirely negative.

At the same time further examination of the blood was made. Smears were stained with Giemsa, Jenner, Gram stain and India ink. Search, carried out for a number of hours, was negative. Hanging drop made from the fresh blood gave negative results. Examinations by means of the ultramicroscope were also negative. Microscopical examinations of laked blood (method of Fried and Sophian) were negative.

February 4, one of the nodes behind the angle of the jaw was excised. This node was the size of a lima-bean, soft on section, succulent, and of a bluish-gray color, with a thin capsule about it. Smears were made from the node-tissue and were examined fresh, suspended in salt-solution, and by the ultramicroscope. No bacteria or other parasites were found. Smears stained with Giemsa, Jenner stain and India ink also showed no form of parasite. Part of the node was fixed in the usual manner, and stained with the ordinary laboratory stains, as well as according to the Giemsa method of section-staining. No parasites were found after careful study of these sections. Histological study of the node showed only hyperplasia and hemorrhage.

Cultures were made from the parenchyma of the node and inoculated on serum-glucose-agar, in glucose-bouillon, on plain agar and on blood-agar, prepared according to the method of Noxy and MacNeal (rabbit-blood, one part; agar, two parts). Anaerobic cultures were also made from the node material, blood-agar and serum-glucose-agar being inoculated. These cultures all remained sterile, except for an occasional colony of *Staphylococcus albus*, which was regarded as a contaminating organism.

#### SYNOPSIS OF CASE

A review of the important features of this case presents the following points of interest:

A young boy was bitten on the scalp by a rat. After an incubation period of two weeks, edema and erythema about the wound occurred. This was soon followed by fever, chilliness, and swelling of the regional lymph-nodes. Incision of the wound did not relieve the symptoms. The patient was admitted to the hospital and treated as a case of erysipelas, on account of the extensive raised edematous erythema which had originated from the wound. Five days after the onset of these symptoms resolution took place and the temperature became normal. Moderate nephritis was present; the spleen was enlarged. This was the end of the first paroxysm.

After a free interval of eight days, swelling of the regional lymph-nodes again took place. Fever, chilliness and dysphagia occurred. There was no erythema. After four days resolution was noted, the spleen and nodes only remaining enlarged. Temperature again became normal.

After a second free interval of ten days the third paroxysm occurred, being characterized again by swelling of lymph-nodes, followed soon by fever, erythema and leukocytosis. Duration of this paroxysm was eight days. Complete resolution of all the symptoms followed, the spleen only remaining enlarged. The urine had become normal.

Throughout the case no marked weakness was noted; emaciation, cachexia and sweating were absent. No nerve symptoms were observed.

Pathological examinations were entirely negative. No parasites were observed.

### III. DESCRIPTION OF THE DISEASE<sup>3</sup>

1. *Definition.*—Rat-bite fever (*Rattenbiss-Krankheit*) (*Sudoke*) is a disease incident on the bite of the rat and followed after a variable incubation period by a single paroxysm or by regularly recurring paroxysms of chills, fever and sweats, lasting a few days, and associated with the occurrence of a local or diffuse bluish-red exanthem. The disease is often characterized by marked nervous symptoms. The course of the malady is signalized by progressive emaciation and weakness; the duration is variable, often very prolonged. Fatal cases are not infrequent. The actual cause of the disease remains unknown.

2. *Historical Survey.*—This disease is best known in Japan; the older, and to us inaccessible, Japanese literature is known to present several cases, collected and published by Katsura in 1890. More recently, in 1899, Miyake<sup>4</sup> published a careful study and analysis of about twenty-seven later cases with the additional facts culled from a personal experience of eleven new cases. Miyake stated that in Japan the disease is a fairly well-recognized one, well understood by the medical profession and dreaded by the laity. It is noteworthy that the older American literature presents many cases sporadically observed and published during the last century, almost all occurring during the settler period of this country's growth, and before the introduction of accurate scientific and bacteriological methods of investigation. An occasional reference to this disease is met in the more recent Scotch, Spanish and French literature, though general knowledge or recognition of the clinical picture is never noted. The German literature presents no cases up to recent years. As a well-defined clinical entity it is thus noted that the disease has remained unobserved and undescribed except by the older Japanese physicians. An analysis of the

3. The facts herein presented are collected from fifty-two cases reported in the world's literature up to January, 1914, and the preceding original case.

4. Miyake: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1899, v, 231.



incidence and symptomatology of the disease is based on the full reports of the following cases:

Japanese .....	24 cases
American .....	17 (including my case)
French .....	2 cases
Scotch .....	1 case
British .....	7 cases
Italian .....	1 case

3. *Etiology*.—A. Incidence: The disease seems to have been observed in America, Spain, France and Scotland. Miyake attributes the frequency of its occurrence in Japan to the simplicity of the abodes in that country, the houses being built of wood; the presence of the rat as a parasite is encouraged by this fact. Its existence during the early days of American settler life is similarly explained by the crudeness of the dwelling-places and the constant presence of the disturbing rat. The complete absence of noted cases in the German Empire is surprising.

B. Occupation: Farmers and people leading agricultural lives are most frequently affected; also seamen, on account of the known tendency of rats to inhabit the hold of ships. All classes of society subject to the bite of the rat, however, are subject to the disease.

C. Age: The age of the afflicted person seems to be variable, the injury being the result of accident, and occurring in those whose means of livelihood or wandering spirit brings them into the haunts of the rat. Grown children, particularly boys, and adult men are the commonest victims. The following figures represent the age incidence:

From 1 to 5 years.....	1 case
From 5 to 15 years.....	10 cases
From 15 to 35 years.....	11 cases
From 35 to 55 years.....	18 cases
After 55 years.....	7 cases

D. Sex: This, depending on the same circumstances, shows a natural predominance of males (males, 31; females, 20).

E. Previous Illness: There seems to be no relationship between any previous disease and the occurrence of this malady; nor does the constitutional condition of the person bitten seem to affect the development or non-development of the clinical picture after the initial lesion. Miyake, in attempting to explain why only certain instances of rat-bite were followed by the development of the typical symptoms of the disease, while others failed to show any deleterious after-effects, was of the opinion that the constitution of the patient at the time of the bite was the deciding factor. This point has not been borne out by any of the subsequent writers or by an examination of the literature of the earlier cases.

F. The Causative Factor: The disease always follows the bite of a rat. The type of animal causing the initial trauma has not been carefully noted; usually it is described as a "large brown" or a "large black" rat; it is almost always noted as large — that is, adult size and form. The white rat and mice, are not known to cause the picture.

The condition of the animal at the time of the injury is not well understood. Some of the most severe results have followed the wounding of sleeping persons by wandering and apparently peaceful animals; in other cases the wound has been dealt by an infuriated animal, fighting to defend its life. The temper of the rat at the time it inflicts the wound does not seem to play a rôle in the incidence or in the severity of the ensuing illness.

The question whether all rats, or only some rats, are able to inflict the disease is also one of interest. It was claimed that only sick rats were infectious; but this hypothesis must remain for the present undetermined, as no instance of the examination of the animal inflicting the injury is at hand; all the animals have remained at large, uncaptured.

Nor is it claimed that every bite inflicted by a rat on a person is followed by the clinical picture shortly to be described, for instances are known in which the same individual on several different occasions had been bitten without evil consequences, while a subsequent bite has resulted in the establishment of a long febrile course with well-marked symptoms. The determining factors, both as regards patient and as regards the rat, remain for future study to identify.

To illustrate the point that the previous condition neither of the rat nor of the afflicted person is a predisposing factor deciding the severity or non-severity of the disease, the following interesting case is quoted from the literature (see Cases 35 and 36):

Two female children aged, respectively, 12 and 9 years, were bitten by the same rat at the same time. The first child developed the disease in a mild form, lasting only four weeks, and intermittent in character. The second child developed an extremely severe type, the temperature being at first continuous, then intermittent, the course lasting four months, and threatening the life of the sufferer.

G. Location of Wound: The site of the injury was as follows:

Face and head .....	11
Hand and arm.....	36
Leg and foot.....	3
Not noted .....	2

There is no evidence that the location of the wound determines the severity of the illness to follow. The face and head injuries seem to run a more severe course, the average incubation period for head and

face injuries being eight days, as opposed to fourteen days for extremity wounds. The average duration of the disease resulting from head injuries is sixty days; from extremity injuries, sixty-six days. The eventual prognosis as to life is unaffected by the site of the wound.

As to the actual nature of the injury inflicted, the severe results seem to follow the more superficial injuries; slight scratches in which not even blood is drawn may be followed by a severe clinical course, while deep penetrating wounds may give rise only to the mildest pictures.

It is also difficult to understand why in a case in which a person receives simultaneously several bites from an animal, all except one injury should become quiescent, while the one shows the typical inflammation and induration associated with the recurring paroxysms.

4. *Pathological Anatomy*.—But little is known on this subject. In practically every case the local wound heals without incidence until the occurrence of the paroxysm, when there is noted a painful swelling and indurated, firm edema about the bite-wound. The nature of the disturbance about this point seems to be of an inflammatory character; vesicle formation may occur; frequently ulceration, superficial or deep, is noted. Occasionally a progressive sloughing or necrosis of the tissues is seen, though the latter grave pathological changes are unusual. A secondary and lasting atrophy of the member may follow the resolution of the process. Suppurative inflammation, or distinct phlegmon, is practically unknown. Examination of the regional lymph-nodes, practiced in a few instances, demonstrated only hyperplasia.

Twice only has a necropsy been performed in fatal cases. The results have been briefly summarized by Miyake as an increase of cerebrospinal fluid and congestion of the pial vessels. No further pathological changes are recorded; detailed post-mortem findings are not accessible. The bacteriological and biological studies gathered from the literature will be discussed in a subsequent paragraph.

5. *Symptomatology*.—The clinical picture of a typical case of rat-bite fever is as follows:

A. *General Description*: The infliction of the wound is followed by an incubation period averaging twelve days. During this time the local lesion usually heals uneventfully and the patient remains unconscious of the fact that he is harboring a pathological process. The first paroxysm is ushered in by a chill or repeated chills, malaise, inability to work; the site of the wound begins to swell, and becomes indurated and bluish-red; the lymphatic vessels stand out inflamed and reddened, and the regional lymph-nodes show early inflammatory enlargement. Within a few hours fever is established, usually from 103 to 105 F.: the pulse becomes rapid and small, the patient much

prostrated. Marked sweating, occurring throughout the paroxysm, marks the remittent drops of temperature. The fever, chills or chilliness and local inflammation continue throughout the duration of the paroxysms. After one or two days, a bluish-red raised exanthem appears on the body, sometimes locally in the vicinity of the wound, sometimes universally. This rash lasts as long as the paroxysm, and disappears with it. Marked nervous symptoms may occur; the reflexes are increased, hyperesthesia or paresthesia is complained of; pareses may appear; dysphagia, muscle pains, etc., may be prominent. The urine frequently shows the presence of a nephritis, varying from mild to very severe. After a variable duration, varying from four to five days, the paroxysm is terminated by profuse sweating.

A free interval now occurs during which the patient is exhausted and suffers from general weakness. He is usually unable to leave his bed or undertake any work. At the end of the free period (from three to five days) the second paroxysm appears, this again being followed by a free interval. This order of alternating paroxysms and periods of release from symptoms continues for a variable period; there may be only one attack, or there may be as many as twenty-six.

The disease usually exhausts its strength as it progresses; the succeeding paroxysms occur at longer intervals, and are maintained for a shorter time, until finally all active symptoms cease. Throughout the course, and long after it, loss of nutrition is marked; cachexia may be severe, convalescence is prolonged and the patient's natural strength returns but slowly.

The fatal cases are severe from the onset; the course is a short and stormy one; nephritis is usually the direct cause of death.

**B. Description in Detail: Incubation Period:** The duration averages twelve days. In the severer and more prolonged cases, this period is shortened to one, two, three or five days; it may, however, be prolonged, particularly in milder cases, to eighteen, twenty-one or twenty-six days. Thus, the incubation period endured one to five days in eleven cases; six to fifteen days in twenty-seven cases; sixteen to thirty-five days in ten cases; sixty days in one case. The relation of the incubation period to the duration of the illness is shown in the following tabulation:

Incubation Period	Duration of Illness
From 1 to 5 days.....	111 days
From 6 to 15 days.....	50 days
From 16 to 35 days.....	54 days

Thus it is seen that the severer and more prolonged cases have a shorter incubation period; in fact, in two cases the incubation period was a matter of hours. These may be regarded as fulminating cases.

In the older Japanese writings, cases are discussed in which the incubation period was said to have extended over from six months to a year, but the facts in these cases remain open to doubt. The two cases reported of symptoms occurring within a few hours of the infliction of the injury (Cases 16 and 41) both terminated fatally.

The incubation period is usually free of untoward symptoms; the wound heals primarily by first intention in the majority of cases, and the bite is forgotten before the first paroxysm occurs.

*Prodromata:* These consist usually of swelling and induration occurring about the site of the healed wound. The lymphatics that drain the area stand out prominently, reddened and tender. Associated with a localized bluish induration there is frequently seen a broad area of edema. The regional lymph-nodes are very soon involved, swollen to the size of a bean or hazel-nut, tender and discrete.

The general symptoms are those of a toxemia; there is malaise, headache, pains in the muscles and back, and tenderness along the main nerve trunks. After one or two days of these symptoms the first paroxysm occurs.

*Onset:* The paroxysm is ushered in by a chill, or chilliness, and a rapid rise of temperature. The temperature may reach 103 or 105 F., remaining practically continuous, with slight remittences, throughout the duration of the active symptoms. The chill may be frequently repeated throughout the course; profuse and drenching sweats are frequent, non-odorous, usually described as "cold sweats." The fever, coming to an end by crisis, is marked by a profound sweat. Occasionally, mild cases are met, described as afebrile. These are uncommon.

The most common type is the intermittent type, in which the fever recurs with every paroxysm and persists throughout its duration. Some of the paroxysms, occurring late in the protracted course of the intermittent type of the disease, may be afebrile, the general symptoms being noted, but fever remaining absent. A continuous type of temperature occurs infrequently. In this variety the disease seems to consist of one prolonged seizure; there are no relapses.

The local changes occurring at the onset have been described above; there are few variations to be noted. Not infrequently in severer forms of the malady a vesicular eruption occurs about the wound. The vesicles may rupture and ulcerate; when this occurs, the ulceration may be progressive and profound; deep sloughing of the edges may be the precursor of a localized gangrenous process, persisting for months and followed by lasting atrophy and disuse of the member. Suppurative inflammation is almost unknown; when it does occur it is always secondary to an open wound which has not received proper attention.

Primary incision of the inflammatory zone occurring locally with each paroxysm, is always futile.

The lymphadenitis is marked, and is, moreover, persistent; the nodes, once swollen, remain so throughout the course of the disease. They partially resolve during the free intervals, only to reassume their inflammatory characteristics just preceding the establishment of each paroxysm.

**The Paroxysms:** Number: There may be only one paroxysm, short and mild; this is the abortive form of the disease. There may be only one attack, but this may be eminently severe and toxic, and end fatally. There usually are from three to ten repetitions of the seizures; as many as twenty-six have been recorded. As the disease progresses, the paroxysms occur at greater intervals and are less severe in nature. The fever may absent itself; when it does, the toxic symptoms are materially modified and more easily borne.

**Duration:** This is usually five days; less often only three days; occasionally, and more particularly in that class of case consisting of one paroxysm, up to twenty days. Prolonged cases beginning with paroxysm of five-day type, may show late in the course paroxysms of one-day type. On the other hand, milder cases may show only repeated one-day seizures, with long intervals separating them.

**Interval:** The interval between attacks averages four days; frequently shorter, rarely longer. An attack occurs always at least once a week; the interval is prolonged as the disease progresses toward a favorable termination.

**Nature of the Exanthem:** It consists of a few large spots, varying in size from that of a dime to that of the palm of a hand, slightly raised or flat circulate spots. The lesions are bluish-red in color, erythematous rather than urticarial.

**Situation:** Usually generalized over the body; often, however, occupying only the region in the neighborhood of the wound. Occasionally vesicles or pustules are observed interspersed with the erythematous spots. A distinct urticarial generalized eruption, occurring toward the end of the course, was twice noticed. A purpuric eruption is once referred to.

**Gastro-Intestinal Symptoms:** The tongue is usually coated and white. Nausea is common with the paroxysms. Constipation is usual; diarrhea not at all infrequent, though usually mild.

Prominence is given in a number of reports to the symptom of dysphagia, coming on early with every recurring paroxysm, completely absent in the interval. It is usually associated with salivation, occasionally with huskiness of the voice, or even aphonia. The dysphagia may be so severe as to resemble rabies, with which rat-bite fever has been confused. The liver and spleen are occasionally enlarged.



**Respiratory Symptoms:** In prolonged and fatal cases, terminal pneumonia has been noted.

**Vascular Symptoms:** No reference is made to acute cardiac conditions as symptoms. Chronic endocarditis is once noted as a complicating factor. Myocardial weakness occurs as a result of the severe toxemia. The pulse is usually recorded as rapid and small.

**Renal Symptoms:** Nephritis was observed nine times in this series of fifty-two cases. It is a severe, often fatal complication; in fact, the most frequent cause of death. The nephritis seems to be of the nature of a glomerular affection of the kidney. The urine shows variable amount of albumin and hyaline and granular casts.

**Examination of the Blood:** See later under Results of Pathological Examinations.

**Nervous Symptoms:** The symptoms referable to the peripheral nerves and spinal cord are frequently encountered and form one of the prominent features of the clinical picture. There is an increase in the tendon reflexes; also stiffness about the joints in the affected extremity; paresthesias and hyperesthesias are common. Extremities may show a lasting atrophy after the cessation of active symptoms. Persistent neuralgic pains, referred to the main nerve trunks, have been noted for years after convalescence.

The highest centers seem to be affected during the height of the morbid process. Marked irritability, associated with rigidity of the neck, is common; this may progress to active delirium or give place to stupor or even profound coma. Reference is made once to the occurrence of hemiplegia.

6. *Course and Duration of the Disease.*—The duration varies from a few days to six months, the average being about two months. The following tabulation presents this more precisely:

Duration	No. of Cases
Less than one week.....	2
From 1 to 4 weeks.....	10
From 1 to 2 months.....	3
From 2 to 4 months.....	6
6 months.....	2
2½ years.....	1

In the case cited by Frugoni<sup>5</sup> (Case 52) the course of the illness was protracted for two and one-half years, though there were long intervals of health between the later attacks.

In order to understand the variability in the symptoms and in the progression of this illness, it is necessary to classify the cases on the basis of the duration of the symptoms and the character of the paroxysms. We may thus recognize the following groups:

5. Frugoni: Berl. klin. Wehnschr., 1912, xlix, 253.

A. *Afebrile Type*: This is a rare form, characterized by the occurrence of subjective symptoms of a mild nature. Neither rash nor nerve symptoms have been observed. The duration is a few days, and the first paroxysm is also the last. These are usually ambulatory cases.

B. *Type with Continuous Temperature*: There are two subtypes. The first is an abortive form consisting of a single paroxysm, associated with fever and marked subjective symptoms; the entire picture disappears in a few days. The second is a severe, usually fatal, form in which the symptoms are initiated by a severe chill or chills, high temperature and oppressive toxic phenomena. The course is progressive, uninterrupted by free intervals; the local symptoms are marked. Nephritis is early established and the fatal issue may occur within one week of the onset of the symptoms.

C. *Type with Intermittent Temperature*: This is the common and most frequently recognized type. It has been fully described earlier in the paper. Its duration is about four weeks, but the paroxysms have been observed even after six months. It constitutes over 50 per cent. of the cases. The progressive and marked cachexia and emaciation constitute one of the most prominent points in the course.

D. *Miscellaneous Types*: Under this heading may be included Case 32, reported by Banker,<sup>6</sup> in which the local symptoms predominate, sloughing and gangrene of the wound being progressive and death resulting from the severity of the nephritis; also Cases 16 and 41, in which the symptoms seem to have been established directly on reception of the injury, or within a few hours. The incubation stage was absent, and the severe toxic subjective phenomena that almost immediately seized the victim culminated in an early death.

7. *Prognosis*.—This is, in general, good. In the series of cases herein cited, fifty-two in number, five (or about 10 per cent.) ended fatally. The majority of cases run a milder or severer intermittent course in which each succeeding paroxysm is weaker than the preceding one, until in time all the symptoms disappear. The loss in strength and weight persists long after the cessation of active symptoms, but it, too, ceases in time. The fatal cases are usually short, violent and stormy in their course; nephritis and marked nerve symptoms early supervene; delirium, stupor and coma attest the severity of the toxic phenomena.

8. *Treatment*.—Until recently it has generally been considered that there is no specific remedy for rat-bite fever. Arsenic in different forms, iron, salicylates, potassium permanganate, have all been used without affecting the course of the disease.

6. Banker: *Am. Pract. and News*, 1886, new series, xi, 70.

The prophylactic treatment has been strongly urged by Miyake. He has used early cauterization with phenol (carbolic acid) in all instances of animal bites, and since utilizing this method has not seen the development of the clinical picture.

In 1912 Hata<sup>7</sup> published his series of cases from Japan, in which salvarsan had been given intravenously. The injections were administered in the course of the febrile paroxysms, usually in the presence of fever, from twelve to ninety days after the bite had been inflicted. The result in all the instances was remarkable, the temperature falling immediately to normal; in only one instance was there a febrile reaction. In two of the eight cases reported, an abortive paroxysm followed the injection; this marked the last of the active symptoms. Twice it occurred that after an interval a relapse took place; in one of these cases a second injection of salvarsan resulted in a complete cure.

Thus it is noted that salvarsan, here as in syphilis, seems to exert a specific influence.

9. *Results of Pathological Examinations.* — Blood-cultures and blood-smears have failed to throw any light on the etiological factor or agent of the disease. The local focus has been repeatedly examined for evidence of parasites, but with the exception of the presence of pyogenic bacteria in one case (sloughing ulcer of the extremity) no offending organism has been ascertained. Excised nodes show hyperplasia and congestion. In one case an excised nodule from the hamstring muscles added no information.

Ogata,<sup>8</sup> in his two cases, has described parasitic organisms in the blood, in smears from excised lymph-nodes, and in smears from the local lesion. These organisms are uniformly similar in nature, and are classed by him among the sporozoa. He has observed them to fecundate and produce sporozoites; merozoites also occur. Ogata further reports favorable results with attempted transmission of the disease to animals; his rabbits were easily inoculated, and not only did not survive the disease, but extirpated glands from these animals inoculated in a second group of rabbits caused the establishment of the characteristic symptoms in the latter. Ogata found the organisms in both of his cases. His work has not been confirmed by the more recent observers.

Examinations of the blood during life show a slight anemia early in the course of the disease; later an advanced anemia becomes established. The white blood-corpuscle count, taken between the febrile paroxysms, is not increased; taken at the height of the fever, there is

7. Hata: München. med. Wehnschr., 1912, lix, 854

8. Ogata: Deutsch. med. Wehnschr., 1908, xxxiv, 1099.

a well-marked leukocytosis varying from 16,000 to 21,500. The relative proportion of polymorphonuclear leukocytes may rise to 87 per cent. An increased proportion of eosinophils may be present, on three different occasions observed to be 8, 11 and 15 per cent.; in another case 5 per cent.

Blood-cultures have failed to throw any definite light on the etiological factor. In addition to the observations of Ogata just mentioned, Middleton<sup>9</sup> (Case 47) reports the finding of a diplococcus once in a blood-smear and culture. Proescher<sup>2</sup> reports the finding of minute bodies in smears of the blood (Case 40).

#### IV. SUMMARY

What is the nature of the disease? Are we dealing with the results of a living parasite, transmitted from the rat to man by means of a bite, or is this a disease caused by the implantation of a peculiar and highly toxic substance?

In the nature of its course it resembles most clearly relapsing fever, the *febris recurrens* of the Asiatics and Europeans. The diseases resemble each other in the intermittency of the symptoms; the incubation period in both is variable. In its favorable reaction to salvarsan the disease has a common factor with both syphilis and relapsing fever, but more particularly with the former. The finding of a spirochete as the cause of both these latter diseases suggests this as the etiological factor in this malady. In the prominence of the nervous symptoms and the post-febrile paralyses, rat-bite fever recalls relapsing fever. The one reported post-mortem examination in this disease revealed a serous meningitis, with increase of cerebrospinal fluid. The irregular paraplegias and atrophies recall the tabetic lesions of lues.

Many authors have indicated a belief in one of the species of protozoa as the etiological factor, but with the exception of Ogata, whose work has unfortunately not been confirmed, such parasites have not been observed. Again, the dysphagia, so marked in Case 25, calls to mind rabies, of late again suspected of being a protozoic disease.

Many of the symptoms of this malady might be the result of a powerful toxin elaborated at the site of the wound and transmitted along the regional nerve paths to the central nervous system, in a manner similar to the propagation of the toxin in tetanus. The extension of the toxin to the posterior ganglions might again recall the dysphagia symptoms analogous in rabies. In the light of a case reported by Banker, the possibility of a neuro-toxin, locally created, must be considered. Banker remarks on the permanent atrophy and

9. Middleton: *Lancet*, London, 1910, i, 1618.

paralysis of the arm only, following on a bite of the hand of the same limb.

To summarize, the point in favor of a spirochete as the causative agent is the similarity of the disease to relapsing fever and syphilis, as regards both the marked nerve symptoms and the apparent curability by salvarsan. In favor of a protozoan cause is the alternation of the paroxysms with afebrile periods, recalling the effects of the malarial plasmodia, though this occurs also in spirochetal diseases.

That the disease is actually caused by living parasites seems strongly upheld by the success of both Proescher and Ogata in inoculating successive generations of guinea-pigs, thus reproducing many of the essential characteristics of the disease.

Appended is a summary of the cases gathered from the literature on which these generalizations have been based.<sup>10</sup>

#### CASES FROM LITERATURE

##### JAPANESE CASES

CASE 1 (Irishawa<sup>11</sup>).—Girl, age 7, bitten on the left index-finger; wound healed in three days. After incubation period of eight days local inflammatory reaction, lymphangitis and axillary lymphadenitis. Two days later, fever. Bluish-red exanthem on arm after seven days. Course, irregular fever, marked delirium and stupor at times. Spleen not enlarged. Urine negative. Duration three months. Recovery.

CASE 2 (Miura and Toriyama<sup>12</sup>).—Woman, aged 32, bitten on middle toe of foot; incubation period fifteen days. Intermittent febrile course; paroxysms three days in duration, introduced by chills and characterized by vomiting, muscle pains, headaches, increased reflexes, peripheral pareses, and mild edema; increasing severity, finally collapse and death. Necropsy reported as negative. No details given.

CASE 3 (Miyake<sup>4</sup>).—Woman, aged 43, bitten between thumb and first finger; superficial wound, healing in three days. Incubation period ten days. Chills, fever, sweat; wound becoming red, swollen and painful. Tongue clouded, moist; pulse rapid; temperature 103 F. Edema of arm and cervical region. Thumb much swollen. Over upper extremity bluish-red exanthem from size of five-cent piece to that of palm of hand. Marked lymphangitis and regional lymphadenitis, general muscle tenderness. Temperature intermittent type, paroxysm three days in duration. Course not followed.

CASE 4 (Miyake).—Man, aged 47, middle finger bitten, next day general reddening of finger. Incubation one week; swelling of forearm; fever and chills and associated typical exanthem. Patient markedly prostrated. Tongue coated. Spleen not enlarged. Course not followed.

CASE 5 (Miyake).—Boy, aged 6, slight superficial bite on nose, inflicted during sleep. Incubation period three days. Swelling of wound accompanied

10. In perusing the literature it has not been unusual to meet with instances of the bite of animals other than the rat. The bite of the cat and of the weasel are distinctly described as giving rise to symptoms similar to the disease under discussion; nor are the results of scorpion and spider bites very much dissimilar.

11. Irishawa: Tokyo med. Ztschr., 1897, xi.

12. Miuri and Toriyama: Tokyo med. Ztschr., 1897, xi.

by chills and fever and appearance of exanthem on face. Slight diarrhea. Pulse rapid. Temperature moderate. Glands of neck swollen, plum-sized and tender; nose entirely swollen. General edema of face. Course, good; no return of symptoms.

CASE 6 (Miyake).—Man, aged 40, bitten seventy days before on nose. Five to six days later face swollen; fever lasting four days. Slight diarrhea present. Prostrated; marked anxiety. Irregular return of fever. Duration about seventy-eight days.

CASE 7 (Miyake).—Man, aged 27, very severe bite on hand. Wound healed uneventfully. Incubation period fifteen days. Paroxysms beginning with repeated severe chills. Fever, malaise and pains in joints; profuse sweating. Swelling of wound; duration of paroxysm not noted. After five days free interval, recurrence. Only at third attack were lymphangitis, lymphadenitis and exanthem noted. Physical examination two months after bite; patient pale, poorly nourished, complained of great pain on movement of right arm. At site of bite dark reddish scar, soft tissues up to elbow swollen, very painful. Exanthem on arm, axilla and neck. Areas of hyperesthesia and increased reflexes. Generally lymph-nodes not enlarged. With the onset of fever, great prostration, oppression, stiffness of neck, headaches. Irregular, intermittent, periodic temperature; interval varying from five to eight days between attacks. After ninth and tenth attacks a general urticaria noted. Result, recovery.

CASE 8 (Miyake).—Man, aged 55, superficial bite on forehead, incubation eighteen days. Onset with fever and prostration followed in three days by the appearance of a generalized exanthem. Physical examination seven weeks later; patient poorly nourished, markedly cachectic, scar of bite bluish-red, infiltrated. Face edematous. Diffuse and profuse erythematous exanthem over body. Cervical glands markedly swollen. Paresthesias. After several attacks, appearance of an urticaria. Course, two and a half months. Result, recovery, except for persistent and marked malaise and emaciation.

CASE 9 (Miyake).—Man, aged 41, slight bite on finger. Incubation period two days, followed by swelling of finger and appearance of fever; slight general edema over body (old cardiac condition). Urine shows albumin and casts. Blood examination negative.

Nephritis disappeared with the cessation of illness. Course not followed.

CASE 10 (Miyake).—Man aged 32, several bites received at same time, arm, cheek and thumb; after twenty-sixth-day interval swelling of arm noted; axillary glands much enlarged. From wound in thumb streptococci and *Staphylococcus aureus* cultivated. Nephritis present. Temperature fell by crisis. Course, intermittent rise of temperature, third paroxysm beginning with subjective symptoms, but only rise of temperature and a few new spots appearing. Result, recovery.

CASE 11 (Miyake).—Female, age not noted, penetrating bite of finger. Incubation period three days. Severe paroxysm lasting twenty days. Physical examination six months after bite: Patient poorly nourished, emaciated, wound entirely healing, cervical glands swollen, sternal tenderness and muscle pains persist; persistent general malaise; every attempt at mild physical exercise followed by rise of temperature.

CASE 12 (Miyake).—Woman, aged 34; patient bitten previously four times by a rat, without sequelae. Ten days after the last bite on hand, pain in wound, swelling and induration. Attacks last five days; recur after three-day free interval. Patient shows marked cachexia, dark induration of wound, marked diarrhea. Paroxysms initiated by chill and rise of temperature; during the height of fever marked stupor. Temperature falls by crisis. Course one month. (No interference remarked with nursing child.)



CASE 13 (Miyake).—Man, aged 30, finger strongly bitten. Incubation interval eight days. Marked diarrhea. After one month pale, cachectic and sick-looking. General circular exanthem. Blood negative. Course not noted.

CASE 14 (Ogata,<sup>8</sup> Tokio, 1908).—Woman, aged 45, bitten on wrist; incubation ten days followed by chills, fever, pain and redness in wound, and local vesicle formation. Three attacks repeated at three-day intervals. At point of injury, bean-sized ulcer formed, with undermined edge; axillary glands swollen.

CASE 15 (Ogata, Tokio, 1908).—Woman, aged 44, bitten on forehead; profuse bleeding, rapidly increasing edema noted. Edema persistent, forehead swollen, eyes closed, deep necrotic ulcer at site of bite. Ulcer covered by black crust. Thick purulent discharge. Cervical glands enlarged. On thigh one large erythematous spot with two tiny vesicles. These latter vesicles contain thick mucoid serum. Complete pathological studies made of blood, ulcers and extirpated glands in both cases. Author found pictures resembling amebic parasites. (See discussion in article.)

CASE 16 (Nishimura,<sup>13</sup> quoted by Miyake).—Woman, aged 63, bitten on left eyebrow; slight abrasion. Next day cold sweat, palpitation. By afternoon of succeeding day dizziness, tiredness, slight, dull pain in wound. Dyspnea, general paralysis; partial suppression of urine, collapse symptoms. Two and a half days after bite swelling of face. Death in collapse on tenth day.

CASE 17 (Taniguchi, quoted by Hata<sup>7</sup>).—Woman, aged 62, bitten on two successive nights on left eyebrow; ten days later infiltration, reddening, and swelling of entire left face, neck and breast; fever and chill; paroxysm lasted four days; returned at intervals of three to four days. Emaciation, infiltration of wound, localized erythema; enlarged regional lymph-nodes; anorexia, headache, delirium, malaise. During fifty days, eight attacks of three days' duration. On third day of each paroxysm always crisis with sweating. Quinin and arsenic without result. After the eighth attack, case regarded as hopeless. Salvarsan 0.4 gm. injected. Only one attack thereafter and then within four weeks patient was entirely well. Later relapse, lasting for four attacks; no particular treatment.

CASE 18 (Taniguchi, quoted by Hata<sup>7</sup>).—Girl, aged 16; three wounds on nose; seventeen days later chill, fever and pain in wound with swelling of face. Fever continues, then intermittent, with two-day intervals. Emaciation, edema of face, swelling of glands, anorexia, etc. Intervals, from two to three days. Duration three days. At third attack 0.4 gm. salvarsan. One attack of fever without subjective symptoms after injection. Then well.

CASE 19 (Katayama, quoted by Hata<sup>7</sup>).—Woman, aged 29; bitten on right cheek; very soon increasing redness, etc.; swelling of glands, fever, anemia, malaise. Incised two weeks later. Thin pus; salvarsan 0.3 gm. intravenously. Complete local and general recovery almost immediately.

CASE 20 (Katayama, quoted by Hata<sup>7</sup>).—Child, aged 10; left foot bitten. Incubation period fifteen days. Edema, swelling, incision and escape of thick pus. Urticaria, fever; necrosis of wound. Fever becomes remittent. Generalized adenitis. Salvarsan 0.3 gm. Immediate critical fall of temperature and patient thereafter well. Recurrence; further course not followed.

CASE 21 (Shibukama, quoted by Hata<sup>7</sup>).—Woman, aged 79, bitten on left arm. Several weeks later swelling, reddening, etc., which gradually disappeared. First rise of temperature two and a half weeks after bite. Seven attacks in one month. Duration of attacks three to four days. Salvarsan 0.6 gm. Recovery immediate.

13. Nishimura: Quoted by Miyake, Note 4

CASE 22 (Sakurane, quoted by Hata<sup>7</sup>).—Woman, aged 37. Left wrist bitten; after ten days, swelling; thirteen days, fever, chill, etc. Salvarsan three weeks after bite, followed by reaction of chill, fever and local pain. Then recovery.

CASE 23 (Shimizu, quoted by Hata<sup>7</sup>).—Girl, aged 2½ years; bitten on right ankle; after one month, swelling, edema, exanthem. Rise of temperature every day. Spleen palpable; localized symptoms greatly exaggerated. Salvarsan 0.09 gm. three months after bite. No symptoms for ten days, then relapse. Salvarsan 0.1 gm. Immediate recovery.

CASE 24 (Yosikawa, quoted by Hata<sup>7</sup>).—Man, aged 22, bitten on finger. Local symptoms marked. Febrile attacks for two months. Then salvarsan 0.4 gm. Rise of temperature to 40.1 C. Immediate fall of temperature. Recovery.

#### AMERICAN CASES

CASE 25 (Watson,<sup>14</sup> 1840).—Seaman, aged 55, bitten over right eyebrow, while sleeping; incubation period two weeks. Swelling of face, neck, painful induration. Marked dysphagia. No constitutional disturbance. No fever noted. Wound scarified; gradual subsidence of symptoms and inflammation; no recurrence.

CASE 26 (Packard,<sup>15</sup> 1872).—Boy, aged 7, bitten on finger; after two weeks redness and swelling; gland in axilla enlarged; wound incised; no pus found. Three days later appearance of erythema over arms, shoulder and body, marked muscle tenderness, high fever; disappearance in five days; occasional recurrence of rash without constitutional symptoms.

CASE 27 (Earle,<sup>16</sup> 1872).—Man, aged 40, bitten on hand. Wound healed in two days. After nine days local reaction. Tongue coated; erysipelatous condition. After four days return of symptoms, local and general. Glands enlarged; chilliness. Iodin used freely. Second paroxysm, duration five days.

CASE 28 (Reece,<sup>17</sup> 1872).—Man, aged 38, farmer; bitten on finger. Incubation period ten days; local reaction, fever, chilliness, malaise; great pain in finger. Iodin used locally. On the fourteenth day, incision, which was negative except for a little yellow serum. On the seventeenth day, dysphagia, soreness of muscles, mental fear. On the eighteenth day, local necrosis; marked sweating. On the twenty-first day, recurrence, perspiration, enlarged glands. On the twenty-ninth day, abscess in axilla of same side; 2 ounces of pus removed. After six weeks patient not entirely well, nervous and weak, easily exhausted; pustular rash appeared lasting several days; marked muscle pain persists; after six months still unable to do any hard physical work. Dyspnea, palpitation and weakness on exertion.

Author quotes another case of bite on shoulder in sleeping baby; diffuse erythema occurred in a few days. General vesicular rash. Duration five days; recovery.

CASE 29 (Banker,<sup>8</sup> 1886).—Man, aged 20, bitten on forefinger. Incubation five days; generalized pains, localizing in twenty-four hours in finger. At local site a tiny vesicle appeared; general darkening and induration of bite. Marked lymphangitis, chills; temperature 105.5; pulse 110. Slimy, mucilaginous saliva. Urine almost suppressed. Marked headaches, sleeplessness, delirium and hallucinations, general erythema and vesicle formation. Duration of first paroxysm, two weeks. After short interval recurrence lasting two months.

14. Watson: New York Jour. Med. and Surg., 1840, iii, 363.

15. Packard: Philadelphia Med. Times, 1872, ii, 408.

16. Earle: Chicago Med. Examiner, 1872, xiii, 3.

17. Reece: Chicago Med. Examiner, 1872, xiii, 5.

General edema and rapid emaciation. After four months lung signs appeared and death occurred. No urine examination. Death apparently due to nephritis, but whether exacerbation of an old nephritis or whether acute nephritis following the rat-bite, not determined.

CASE 30 (Banker, 1886).—Woman, aged 35, bitten on hand. After three days pain in wound; after ninth day soreness and swelling of finger; marked lymphangitis. Incision of local site; no pus obtained. Induration, swelling and lymphangitis persisted for two months. Atrophy and hemiplegia of same extremity occurred, atrophy remaining almost permanently. Persistent neuralgic pains occurred down arm indefinitely afterwards.

CASE 31 (Banker, 1886).—Woman, finger; incubation period ten days; purplish vesicle appeared locally; typical course and symptomatology. Secretions noted as being checked. Marked sleeplessness; occurrence of generalized erythema. Course four weeks; no relapses.

CASE 32 (Banker, 1886).—Woman, aged 70, bitten on hand; five days' incubation; wound did not heal for six months; constant sloughing; early dropsical symptoms; death. No necropsy.

CASE 33 (Cook,<sup>18</sup> 1885).—Boy, aged 11, bitten on right hand by an enraged and caged animal. Incubation two weeks. Generalized edema. Marked lymphangitis. Generalized purplish erythema. Fever and diarrhea. General enlargement of all glands of body. Result, recovery.

CASE 34 (Evans,<sup>19</sup> 1901).—Boy, aged 8, hand; incubation period two weeks; local and general reaction lasting one day only. After this, every week for nine weeks had recurrence of fever and constitutional symptoms lasting two to three days. Third week appearance of general erythema. Hemoglobin, 70 per cent.; red blood-cells, 4,200,000; white blood-cells, 16,200; polymorphonuclears, 87 per cent.; lymphocytes, 85 per cent.; eosinophils, 5 per cent.; blood-culture, *Bacillus subtilis*. Course, recovery.

CASES 35 AND 36 (Evans, 1901).—Girls, aged 12 and 9 years, bitten at same time by same rat. Three weeks later on same day both took sick, temperature 105 F.; both seats of injury swollen. Older child for four weeks had paroxysms lasting one day, with local swelling, fever and erythema; younger child had continuous fever for six weeks, then intermission first of one, then of a few days, then of a week; well in four months; marked exhaustion following.

CASE 37 (Wilcox,<sup>20</sup> 1839).—Man, aged 40; bitten on root of thumb; incubation twelve to thirteen days; three paroxysms, lasting four to five days each, with four days free interval; subjective symptoms very severe, with delirium. Constipation noted. Local slough of bite. Recovery.

CASES 38 AND 39 (Gilliam,<sup>21</sup> 1869).—Mother and son, both bitten by rat at night. Superficial abrasion; two weeks' incubation. Child showed swelling of finger and fever. Two days later similar symptoms noted in mother. Mother's finger advanced to slough, finally healing. Child showed enormous tender swelling of finger, marked constitutional symptoms, irritability of stomach and intestines, erythema, blotches on skin, malaise and finally death. Child was bitten in two places, but the bite that did not bleed was the site of the inflammation.

CASE 40 (Proescher<sup>2</sup>).—Boy, aged 7, superficial bite on dorsum of hand; after ten days walnut sized swelling, slight tenderness. On upper and lower arm pale, bluish-red areas of regular outline; regional glands enlarged. Liver and spleen not enlarged.

18. Cook: Indiana Med. Jour., 1912, ii, 77.

19. Evans: Tr. Chicago Path. Soc., 1901-1903, v, 298.

20. Wilcox: Am. Jour. Med. Sc., 1839, xxvi, 245.

21. Gilliam: Cincinnati Lancet and Observer, 1869, xii, 16.

Red blood-cells, 4,700,000; white blood-cells, 8,000; polymorphonuclears, 77 per cent.; eosinophils, 1.1 per cent.; myelocytes, 0.8 per cent. Wound punctured and slight bloody fluid obtained.

On twenty-first day after bite, sudden rise of temperature to 105 F., maintained for one day. Fall of temperature by crisis, and remaining at normal [caused by puncture (?)]. During fever, white blood-cells, 21,500; polymorphonuclears, 78 per cent.

Excision of wound site. Second rise of temperature to 101 F., lasting only a few hours. Arsacetin  $7\frac{1}{2}$  grains given hypodermically. Second injection of 15 grains given same day.

Albumin and hyaline casts in urine.

Two months later boy well, but urine still showing albumin and hyaline casts.

*Pathological Examinations.*—Peculiar formations in red blood-cells, contained in hemoglobin-free zone; they consist of minute formations of deep red color, refracting light. Also larger formations, 2 to 3 microns in size. In one cell, appearance of mitosis seen. No bacteria or protozoa found. Anaerobic and aerobic cultures negative. Anaerobic and aerobic cultures of tissue negative.

*Pathologic Changes in Tissues:* Young connective tissue elements; proliferation; endothelial cell increase, clasmocytes. Hyaline changes in walls of small blood-vessels. Tremendous number of bacteria seen in sections.

*Animal Experiments.*—Excised tissue inoculated into four rats with negative results. Tissue injected into guinea-pig; developed small abscess at site of inoculation and general lymph-node enlargement. Also eruption.

#### FRENCH CASES

CASE 41 (De Micas,<sup>22</sup> Toulouse, 1895).—Man, aged 50, bitten on finger; same evening chill and sweat; delirium all night. Two days later very sick, dry tongue, edema of extremity. Local swelling incised; no pus obtained. Improvement in wound; edges of incision appearing bluish black and congested as if following application of a Bier bandage. Pulse rapid and small; temperature 104 F. Generalized raised eruption over body, in places vesicular; almost complete anuria, edema, delirium, lumbar pains. Tongue very dark red. Urine shows large amount of albumin. On seventh day death from uremia. No lymphangitis noted. Toxic death.

CASE 42 (Millot-Carpentier,<sup>23</sup> Paris, 1883).—Boy, aged 20, bitten in four places by angry rat, once in arm and three on hand; very superficial, no blood drawn. On fifth day pain in hand, fever, chilliness, sweat. Small typical phlegmon appeared, disappearing after twelve days. After free interval of a few days return of local and general symptoms. Marked dysphagia. Congestion of face, intense fever, hoarseness, almost aphonia, marked salivation, paroxysms all end by crisis, progressive paroxysms milder. Paroxysms recur every third day, lasting several hours, and leaving patient markedly prostrated. Three months after bite, patient was still having occasional crises, preceded by aura or pain in finger. Large violaceous swelling of thumb; generalized ecchymotic rash over body. Characteristic is the temporary dysphagia occurring with each paroxysm.

#### SCOTCH CASES

CASE 43 (Carter,<sup>24</sup> Edinburgh, 1907).—Man, aged 40, bitten on finger; wound healed. After two days incubation, redness, lymphangitis and lymphadenitis. Course very prolonged—six months. Twenty-six attacks in all; interval two

22. De Micas: Arch. méd. de Toulouse, 1895, i, 170.

23. Millot-Carpentier: Union méd., 1883, xxxviii, 1069.

24. Carter: Edinburgh Med. Jour., 1907, new series, xxi, 443.

days; duration three days. Later duration of attacks only twenty-four hours. Paroxysms characterized by languor, weakness, nausea, thirst and dry skin, ending suddenly with profuse sweat and critical drop of temperature. Early attacks associated with stiffness of arms, neck and masseter muscles. Patchy erythematous eruption on shoulders and chest during attacks, fading with disappearance of fever; spasm in throat and difficulty in swallowing complained of during attacks. Cervical lymph-nodes enlarged. Two small subcutaneous nodules noted on forearm and calves of legs, reappearing with attacks. Spleen enlarged. White blood-cells, 16,000. Blood culture negative.

## ENGLISH CASES

CASE 44 (Horder,<sup>1</sup> 1910).—Man, aged 62, bitten on thumb, superficially; had received ferret's bite the same day. Both wounds healing without swelling. Incubation period three weeks. Induration and lymphangitis appearing about site of the rat-bite. Temperature 101 F. Malaise; duration three days. After interval of four days recurrence of paroxysms, throat husky, hands swollen, delirium; no swelling of glands; diffuse erythema; liver and spleen not enlarged. White blood-cells, 18,000. Temperature 102 F. Pulse, 84. Course, five recurrences, two or three days apart. Three-day duration. Characterized by anorexia, torpor, sore throat, hoarseness; nodule in hamstring muscle noted. Blood culture negative. Animal inoculation with blood. Excision of nodules. Urine examination, blood smear examination, all negative.

CASE 45 (Horder, 1910).—Man, aged 52, seaman, bitten on thumb; two weeks after attack recurrent paroxysms occurring every five to six days. Chills and fever. Temperature 103 F. First paroxysm severe, later milder and occurring at longer intervals. No enlargement of glands or spleen. White blood-cells, 19,000. Blood-culture and smears negative. Duration, eight weeks ending in recovery.

CASE 46 (Horder, 1910).—Man, aged 55, farmer, bitten on elbow; after twenty-eight days, fever; duration four months, characterized by periodic recurrences of fever; no skin eruption.

CASE 47 (Middleton<sup>2</sup>).—Girl, aged 3; left hand bitten while asleep; incubation period of fourteen days followed by swelling of wound and a lump in axilla. Febrile paroxysms lasting forty-eight hours, with sweating, prostration, no pain. Before each paroxysm, swelling of wound and glands. Interval between attacks two or three days. Temperature 105.4 at the highest. Eight attacks in all; never less than two days in duration. Red, patchy, measy rash over cheeks, forehead and legs with the attacks. Eventually well.

Blood examinations negative, except for diplococci found on one occasion. Diplococci also found in one instance in blood culture. Organism not studied.

CASE 48 (Nicholson<sup>3</sup>).—Boy, aged 10, trifling bite on left hand; five weeks of careful medical attention. Then urticaria of legs, body and face. Swelling of back of arm, hand and elbow; no pus found. Antistreptococcus serum used without visible result. Course almost five months; irregular paroxysms lasting one to two days; one lasting fourteen days. Gradual diminution of strength of attacks. Well.

CASE 49 (Hewlett and Rodman<sup>4</sup>).—Man, aged 23, bitten on left finger; two months later development of axillary gland. Fever every five days, recurring for seventeen weeks. Duration of paroxysm from two to five days. Fall of temperature by crisis. Erythematous rash on chest and arms. Glands in axilla and groin.

Blood examination and blood-culture negative for parasites.

25. Nicholson: Practitioner, 1913, xci, 429.

26. Hewlett and Rodman: Practitioner, 1913, xci, 86



CASE 50 (Cruikshank<sup>27</sup>).—Man, aged 51; bitten on finger. Sucked wound. Rat said to be "mangy" or sick. Thirteen days later bluish discoloration, then almost black. Brawny induration; tenderness, no fever; purplish rash on arm. Gangrene of entire finger; amputation required; healing took place.

Eight days after operation, or twenty-eight days after bite, headache, fever chilliness, nausea, and purplish rash again appears on arm. Temperature from 99 to 102 F. Delirium. In fifteen weeks fifteen attacks. Periods between attacks from five to eleven days. Paroxysms three days in duration. Urine negative. Convalescence very slow; after six months still unable to get about.

CASE 51 (O'Carroll<sup>28</sup>).—Man, aged 36; bitten on lower lip while asleep; moderate bleeding. Two days later lip swollen, edematous, purple. Seven days after this, admitted to hospital. Huge edema of lip, chin, etc. Submaxillary and sublingual glands enlarged and tender. Relapsing type of fever established; duration of fever from three to four days. Intervals from three to four days; irregular temperature; highest 103.8 F., subnormal usually after cessation of relapse. During fever, malaise for six weeks. When discharged from hospital urine negative. Developed edema of legs and face. Albumin and hyaline and granular casts with red and white blood-cells in urine. Pale, marked secondary anemia; pronounced emaciation. Parenchymatous nephritis present.

White blood-cells, 7,200; polymorphonuclears, 88 per cent.; eosinophils, 15 per cent.; myelocytes, 1 per cent.

Four months after bite, anemia and nephritis were marked; pleural cavities aspirated and clear fluid obtained. Improvement began soon after, and one year later entirely well.

Five weeks after inoculation animal killed. Necropsy showed lymph-gland enlargement, no bacteria or protozoa.

#### ITALIAN CASES

CASE 52 (Frugoni<sup>2</sup>).—Farmer, aged 54, deeply bitten on thumb; wound healed in three days. After fifteen days, sensitive red swelling of wound, breaking down to a small ulcer. Entire thumb much swollen. Chill, vomiting, fever, headache. Irregular remittent fever lasting fifteen days. Axillary and inguinal glands already swollen; large wine red spots appear on extremities. Skin infiltrated and elastic; painless.

Free interval of from twenty to thirty days.

Reappearance of fever at irregular intervals during one year. At end of year, reappearance of skin manifestations with much weakness and severe cramps in calves of legs. Same attack again in five months and again in one year. Sudden right-sided exophthalmos two and one-half years after bite. Enlargement of glands, erythematous exudation, fever; exophthalmos marked, injection of conjunctival vessels, chemosis, sight good, fundus oculi, negative. Urine negative. Red blood-cells, 3,100,000; hemoglobin, 70 per cent.; white blood-cells, 8,700; polymorphonuclears, 60 per cent.; eosinophils, 8 per cent.; mononuclears, 10 per cent.; lymphocytes, 22 per cent. No parasites. Eosinophilia later, 11 per cent. Exophthalmos disappeared slowly. Wassermann, blood and stool negative.

Patient became and remained apyrexial.

Returned later with new eruption. One erythematous spot punctured; spreads negative. Cultures negative. Cure.

27. Cruikshank: *Brit. Med. Jour.*, 1912, ii, 1437.

28. O'Carroll, Joseph: *Dublin Jour. Med. Sc.*, 1912, cxxxiii, 214.



## ADDENDUM

The following case<sup>29</sup> while appearing too late to receive mention in the text, has been added because of its unusual interest:

Hindoo woman, bitten eight years ago on right ear; ulcer of ear for three months. Fourteen days after bite, attacks began to occur, three to seven days in duration, continuing to the present time. Temperature to 105 F. Anemia and puffiness of face. Rash, glands, nephritis, and erythrocytes in urine. Wassermann negative.

Neosalvarsan 0.7 gm. given intramuscularly. After one week patient was well; no more attacks.

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29. Surveyor: Lancet, London, 1913, clxxxv, 1764.

FACTORS INVOLVED IN SOME CASES OF PLEURAL  
FLUID ASSOCIATED WITH NORMAL OR  
INCREASED VOCAL RESONANCE \*

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Of the many complicated problems in the field of the mechanism of the physical signs of the respiratory system, perhaps none has been so admittedly puzzling, particularly in adults, as that of the normal or increased vocal resonance sometimes encountered in cases of pleural effusion. Skoda thought he had solved the riddle by attributing the phenomenon to what he calls consonance, but his explanation is untenable. The literature on the subject is, for the most part, rather suggestive than really helpful. Walshe's statement is: "Sometimes explicable by solid adhesions conveying the vibrations from the lung to the chest wall; in other instances the anomaly does not admit of explanation."

In trying to obtain any explanation — and only one will be offered here — for the occurrence of normal or increased vocal resonance in cases of pleural effusion, it is necessary first of all to have some knowledge of the factors operating in those cases of effusion in which there occurs a diminution or absence of vocal resonance. Assuming that in most cases of pleural effusion the compressed lung still retains more or less air in the alveoli, an occurrence which is certainly very often encountered, and which we find in experimentally produced effusions in which the conduction of sound is impeded more on the side with the effusion than on the normal side, it is not difficult in these cases, with some air still remaining in the lung, to locate a place where much of the loss of sound might occur, namely, at the junction of the lung with the fluid. Experimentally, it can be readily shown that a marked "break" does occur as sound passes from such an air-bearing lung to fluid. This "break" is apparently largely due to the change of mediums, the air-borne sounds within the lung having to pass from air, which is a very light medium, to fluid which is a very much more dense medium. The loss of sound is not nearly so great as it passes from the fluid to the chest wall. A second factor in diminishing the sounds after they leave the lung is that of diffusion. The intensity of the sounds immediately after entering the fluid as compared to the intensity after

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the sounds reach the chest walls is, in a general way, inversely proportionate to the area of visceral pleura exposed to the fluid in comparison to that of the parietal pleura bathed by the fluid. Recognizing the important part the lung plays in the interference with sound conduction in cases of effusion in which the vocal resonance is diminished or absent, the next logical step in trying to explain those cases exhibiting a normal or increased vocal resonance is to test out other conditions of the lung, to see if any of them might under the circumstances contribute more favorable factors to the conduction of sound.

The condition of the lung offering perhaps the most marked contrast to the air-bearing lung is the completely solidified lung. Having no case to report in which the patient presented before death a normal or increased vocal resonance, and at necropsy a "solid" lung surrounded by fluid, we are obliged to resort to other means for determining whether a "solid" lung would be favorable to the conduction of sound in cases of pleural effusion.

Our most illuminating experiments along this line have been with the chests of fetal calves near term. The alveoli in such animals being free from air, we are enabled to deal with one type of "solid" lung. Sounds introduced into the trachea of such an animal reach the external chest surface with great distinctness. If fluid is introduced into the pleural cavity of a fetal calf till it is completely filled, the sounds at the periphery of the chest will be found to have undergone comparatively little change, being still very distinct, while if the water in the pleural cavity is replaced by air, the sounds at the external chest surface will be found to have undergone a very marked diminution. If the fetal chest contains fluid and the lung is inflated, the sounds at the periphery of the chest will be found to be much weaker than while the lung was still air-free.

An experiment comparable to the foregoing with comparable results can be performed with the fetal lung outside the body. If the fetal lung is submerged in a vessel containing water, and sounds are introduced into the trachea and if a stethoscope is used, the mouth of the bell being tightly covered with a piece of liver to represent chest wall, and if this liver is likewise placed in contact with the water, but at no point touching the lung, the sounds will be heard with great distinctness after having passed through fetal lung, water and liver. Very much weaker sounds will be obtained if the fetal lung is replaced by an air-bearing lung.

Another experiment closely resembling the preceding ones can be made by replacing, in the last experiment, the fetal lung by a heart. Sounds after entering the aorta and passing through the cardiac walls,

the fluid and the liver covering the inferior opening of the stethoscope, still retain considerable intensity.

One can readily become convinced of the facility with which sounds pass from "solid" tissue to water by applying a suitable cylinder to the chest wall of a living human being and inserting water into this cylinder so that it is in contact with the chest wall, while the opposite end of the cylinder is tightly joined to the bell of the stethoscope. The vocal resonance and the respiratory murmur, though diminished, will be very distinctly audible.

How closely do our experiments parallel conditions that may occur in the human subject? In each experiment except the last, as contrasted with the human being, there are three things to be compared: the chest wall (or its representative, liver), the fluid and the lung. The fetal calf's chest wall corresponds sufficiently closely to the adult chest wall. Even if it is, so to speak, made thicker by overlaying it with liver, much of the sound intensity is retained. As for the fluid, conditions are relatively much alike in both the experiments and in the supposed clinical case. The amount of diffusion by the fluid may be alike in both cases. Any striking difference, then, in the acoustic phenomena in the experiments and in human beings must relate to the lungs themselves.

The great bulk of the soft cellular tissues, whether normal, inflammatory, or malignant, apart from their fluid contents, is composed of substances known as gels. These gels, of which gelatin in a 10 or 20 per cent. strength in the firm state is an example in pure form, are closely allied in their general physical characteristics, and one would expect this similarity to extend to their acoustic properties. This has been just what has occurred in all our experimental work. We have had sufficient material for experimentation in the shape of fetal lung, liver, and muscle, and though more restricted in obtaining "solid" material from hepatized lungs, experimentation and inference show that such diseased tissue in its sound-conducting properties closely resembles the soft tissues of the body, including the fetal lung.

All our evidence indicates that these various substances, liver, muscle, fetal lung, and hepatized lung greatly resemble one another in the following particulars: They are all fairly good conductors of sound. In a general way they considerably resemble one another in their conductivity of sound. When one or more of these materials are placed in apposition the resultant effect on sound conduction is much the same as if a similar amount of any single one of these materials had been used, indicating that no serious "break" occurs as sound passes from one of these substances to another. Finally, in their relation to air and water they all resemble one another closely; that is,

there is a marked loss of sound as it passes from air to any of these substances, while there is very much less loss of sound as it passes from these various substances to air, and the passage of sound from these substances to water or in the reverse direction is attended with no serious loss of sound due to the change of mediums, because they are not of sufficiently different densities. We conclude, therefore, that these various materials, liver, muscle, fetal lung, and hepatized lung, may be considered for our purposes to be one single medium, and to act practically alike in their relation to sound conduction, whether by themselves or in association with other mediums.

While our chain of evidence is not absolutely complete as far as the lung affected with solid infiltration is concerned, all available evidence indicates that it corresponds acoustically to fetal lung and other gels.

The fluid contents of these various substances does not materially affect their conductivity.

When a pleural effusion exists there may be associated either one of two types of "solid" lung; first, that in which there is no infiltrative process, but from which the air has disappeared as the result of pressure or absorption, leaving a lung closely resembling the fetal type; and, secondly, the lung which is "solid" as the result of inflammatory or malignant change. The airless but otherwise normal lung would, on account of its smaller bulk, probably offer more favorable opportunities for sound conduction than a hepatized lung, provided that in the two cases the bronchi were equally patulous.

It is possible, according to Skoda, for only a portion of a lung to become airless as a result of an effusion, and to sink beneath the surface of the fluid.

If our conclusion is correct, that the tissue of a lung "solid" either from compression or actual pulmonary disease closely resembles fetal lung tissue acoustically, it is clear how the vocal resonance might be normal or increased in cases of pleural effusion. An increase in the vocal resonance in cases of consolidation of the lung is the usual clinical finding, and as long as the bronchi remain patulous the mere presence of fluid between the "solid" lung and the chest wall should not very materially affect the transmission of sounds, except through diffusion, though the change of medium from "solid" to fluid, and from fluid to "solid," would exert more or less of an effect. The reasons that no great change except that due to diffusion should take place are, first, that water itself is a good conductor of sound, and, secondly, that sound vibrations do not suffer greatly in intensity as they pass from "solid" tissue to water or from water to "solid" tissue. This latter fact might be expected to occur, because water and "solid" tissue do not differ greatly in density; but the same thing can be readily demon-

strated by a great variety of experiments, such as those of the fetal calf and the others presented above.

Our conception, then, of what we believe occurs in some cases of pleural effusion with a normal or increased vocal resonance may be summarized as follows: The sounds reach the surface of the "solid" lung with a certain degree of intensity, which is naturally greater than would be encountered at the external chest surface in a case of pneumonia without effusion, because the sound has not yet passed through the chest wall. The intensity of sound at the lung surface will vary to some extent with the amount of lung tissue that is traversed, so that we would expect to find louder sounds at the surface of a lung that is airless as a result of compression than in one that is "solid" from infiltration. The vibrations then enter the fluid, and do this without any serious "break" as a result of the change of medium. In their course through the fluid comparatively little sound is lost except that due to diffusion, because of the excellent conducting properties of fluid. Finally, the vibrations enter the chest wall, and again effect a transfer of medium without great loss of intensity. In other words, the interference in sound conduction is not very greatly different, as a result of the fluid in the pleural cavity, from a case presenting a "solid" lung without any effusion, provided the bronchi remain patulous, except for the loss due to diffusion. It is certainly true that the conditions for sound transmission are much better in a case with a "solid" lung surrounded by fluid than in a case of effusion in which the lung still contains air, or in a case of pneumothorax, whether the lung is either "solid" or air-bearing, provided there is no perforation from the lung into the pleural cavity.

If our explanation is correct, why does not this phenomenon occur oftener? As a matter of fact, it is impossible to state just how often a normal or increased vocal resonance does occur in cases of pleural effusion. Small basal accumulations of fluid overlying "solid" lung giving a normal or increased vocal resonance, are probably not very rare. As to the actual causes for the infrequency of the phenomenon, they may be considered to lie chiefly in the lung substance or in the bronchi. We have already spoken of the marked loss of sound that occurs when a lung, still retaining air in the parenchyma, is in contact with fluid. Interference with sound transmission from bronchial obstruction might, theoretically, be caused either by pressure from without, thus bringing the bronchial walls in apposition, or by edema or other abnormal fluid within the bronchi, which, through the action of fluid, or fluid and air, that is, froth, would occasion an intrabronchial obstruction to the passage of sounds.



Our conclusions are offered in explanation of only some of the cases of pleural effusion manifesting a normal or increased vocal resonance, for we do not believe the explanation holds good in all cases, and especially in children we believe that other causes may operate.

The loss in intensity due to diffusion in both the air-bearing and "solid" lungs will be rendered less by whatever allows the lung to approach closer to the chest wall.

The conclusions apply to various forms of fluid in the pleural cavity, whether serous, purulent or hemorrhagic (fluid blood).

The experimental evidence on which the conclusions are based has been reduced to a minimum amount of space, but we trust that it is sufficient to elucidate the subject in hand. The experiments in full will be given elsewhere.

This subject has clinical as well as theoretical interest. Thus, in any case of a doubtful nature presenting a normal or increased vocal resonance, the idea of fluid in the pleural cavity should be entertained; and, given a case with demonstrable fluid in the pleural cavity exhibiting clinically a normal or increased vocal resonance, the possibility of there being "solid" lung beyond the fluid should be borne in mind. While in some cases such a "solid" lung may be simply a compressed and airless lung, the other alternative is also to be considered, that the lung may be affected with inflammatory or malignant disease. If the condition is a recent one, recently developed consolidation of the lung in addition to the fluid is to be suspected.

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## THE RELATION OF URIC ACID TO GOUTY ATTACKS\*

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The work recorded in the present paper, although begun with another purpose in mind, is the result of an attempt to find *if there is any relation between attacks of gout and the amount of uric acid in the blood, or between such attacks and the amount of uric acid excreted in twenty-four hours*. By means of the new method of Folin<sup>1</sup> the surmises of earlier investigators that the uric acid content of the blood is increased in gout has been confirmed by Dr. Folin<sup>2</sup> and coworkers in a certain number of cases. These findings, taken together with observations showing a retardation of uric acid in gout, are in accord with the hypothesis of Gerrod<sup>3</sup> that the attacks of gout are due to increase of the uric acid content of the blood above its saturation point as a result of the inability of the kidney to excrete uric acid. Our original point, one in practical therapeutics, was to determine how we could influence the metabolic perversion, especially by dietetic measures. When our preliminary observations did not show a greater amount of uric acid in the blood of gouty patients than in normal subjects, nor any relation between uric acid excretion and the attacks of gout, and finally, showed that attacks of gout appeared even when we artificially lowered the uric acid content of the blood with atophan, we gave up our original purpose in order to reexamine carefully these points concerning the relation of uric acid excretion to gout.

The investigation was carried out on two women, Mrs. W. and Mrs. L., both of whom gave typical histories of gout—repeated sudden afebrile attacks of swelling, pain, heat and redness localized in one or more joints, which gradually subsided after several hours—and on Roentgen-ray examination showed bony changes—Bruce's nodes—characteristic of gout. It is important to emphasize that these patients were not cases of atrophic arthritis or hypertrophic arthritis, or infectious arthritis, but cases of real gout, carefully selected after consultation with our orthopedists.

Throughout the investigation the patients were kept on an approximately constant, purin-free diet—54.8 gm. protein, 67.5 gm. fat and

\* Submitted for publication Jan. 19, 1915.

1. Folin and Denis: Jour. Biol. Chem., 1913, xiii, 469.

2. Folin and Lyman: Jour. Pharm. and Exper. Therap., 1913, iv, 539.

3. Gerrod, A.: The Nature and Treatment of Gout and Rheumatic Gout, London, 1859.

167.5 gm. carbohydrate, a total of 1,496 calories — sufficient to maintain the patient's weight. The diet was made up of 150 gm. bread, 136 gm. egg, 526 gm. milk, 13 gm. butter, 120 gm. potatoes, 29 gm. rice, 20 gm. sugar, 2 slices cucumber and 2 leaves of lettuce per day. These raw materials, given in the form of a prescription to the dietetic department of the hospital, were used as the basis of menus which made a very attractive and varied diet for the patients. We would like to call especial attention to this method of prescribing a very strict, weighed diet over a long period, with entire satisfaction to the patient. By cooperation of chemist and dietitian both scientific accuracy and palatability can be obtained. One of our patients was confined to bed on account of an old ununited fracture; the other sat up part of the day.

After the preliminary work showed that the excretion of uric acid and creatinin was to be the object of our study, it was appreciated that criticism might be made of the completeness of the twenty-four-hour urinary specimens. Great care, therefore, was directed to this point. Satisfactory collections of complete twenty-four-hour quantities of urine, though seemingly a very simple matter, is in actual hospital practice exceedingly difficult. The constancy of the creatinin and uric acid determinations in twenty-four-hour quantities of urine collected from other patients as well as the constancy of the uric acid output in our patients when no drug was being given (Mrs. W., days 15 to 40) convinced us that we were surprisingly successful in our efforts. For this we have to thank the executive department of the hospital for unusually active cooperation and every facility for the strictest supervision of the patients. The patients and nurses were interested and cooperated with us completely in the work. The patients were kept in a small room by themselves and one of the nurses volunteered twenty-four-hour duty, sleeping in the same room and never leaving the patients. Even the small quantities of urine usually unavoidably lost with the feces were collected, thanks to nurse and patients. The urines were preserved with thymol and chloroform (5 c.c. chloroform and 5 c.c. of 5 per cent. thymol solution to each 1,000 c.c. of urine).

The uric acid in the blood was determined by Folin's method. A small, hollow, sterile needle about a millimeter in diameter, which had been rinsed with a solution of paraffin in ether, was inserted into the vein at the bend of the elbow and the blood allowed to flow directly into a weighed 50 c.c. Erlenmeyer flask containing 0.1 gm. potassium oxalate. This proved to be a simple method, which avoided transferring the blood from a syringe. By this means a better flow of blood was obtained with less danger of clotting than when suction of any kind was used. A tourniquet, made of a piece of rubber tubing or a

TABLE 1.—URIC ACID, CREATININ, AND CREATIN EXCRETION OF A GOUTY PATIENT

Mrs. W., weight 59.1 kilos.

Day	Urine						Blood	Ato- phan* No. Doses Daily	Attacks
	Total Quan- tity	Sp. Gr.	Total Nitro- gen, Gm.	Uric Acid, Gm.	Creat- inin, Gm.	Crea- tin as Creat- inin, Gm.	Uric Acid Mg. Per 100 Gm.		
Prelim- inary	....	....	....	....	....	....	....	....	Severe in finger and wrist joints.
1	568	1.016	2.36	0.186	0.324	....	....	....	
2	1,120	1.01	5.64	0.209	0.412	....	{ Taken at 12 m. 2.10 }	2†	
3	670	1.012	5.26	0.314	0.45	....		6	
4	840	1.01	6.40	0.225	0.349	....	....	6	
5	1,270	1.011	6.40	0.408	0.512	....	0.66	6	
6	900	1.008	2.58	0.132	0.187	....	....	6	
7	720	1.011	3.43	<b>0.196</b>	<b>0.324</b>	....	....	6	Attack beginning 9 a. m., lasting till p. m. Left fingers and wrist.
8, 9, and 10:	High purin diet.....						....	6	
11	880	1.013	4.98	0.31	0.60	....	....	6	
12	1,740	1.008	5.92	0.58	0.60	....	....	6	
13	1,060	1.013	5.04	0.36	0.72	....	....	6	
14	1,060	1.012	5.44	0.38	0.46	....	....	3	
15	1,020	1.016	6.33	<b>0.316</b>	<b>0.693</b>	....	....	0	Moderately severe attack 7 a. m. - 10 a. m. Left wrist and finger joints.
16	1,160	1.011	5.85	<b>0.233</b>	<b>0.33</b>	....	....	0	Attack 6 a. m. Left wrist and finger joints.
17	1,230	1.0115	6.06	<b>0.27</b>	<b>0.43</b>	....	2.02	0	Attack. Same joints.
18	1,420	1.011	7.47	0.25	0.51	....	....	0	
19	720	1.016	7.18	0.289	0.51	....	....	0	
20	1,060	1.013	7.00	0.30	0.51	....	....	0	
21	2,100	1.01	8.73	0.42	0.54	....	....	0	
22	900	1.017	7.44	0.182	0.52	....	....	0	
23	1,100	1.012	7.51	0.281	0.51	0	....	0	
24	1,140	1.01	7.32	0.30	0.48	....	....	0	
25	1,090	1.008	7.25	0.301	0.54	0	....	0	
26	890	1.008	6.67	0.264	0.52	0	....	0	
27	1,260	1.008	7.50	0.294	0.52	0	....	0	
28	1,230	1.008	6.90	<b>0.32</b>	<b>0.518</b>	<b>0.08</b>	....	0	Very moderate at- tack 6 a. m.-11 a. m.
29	1,120	1.01	6.64	<b>0.294</b>	<b>0.49</b>	<b>0.06</b>	....	0	Severe; went down in p. m.; on in eve- ning and next morning.
30	1,440	1.01	7.20	<b>0.305</b>	<b>0.54</b>	<b>0.12</b>	....	0	Attack passed off about noon.
31	1,660	1.011	7.24	0.287	0.52	0.06	....	0	

\* Each dose 0.5 gm. † Began 5 p. m.

TABLE 1.—(Continued)

Day	Urine				Blood			Ato- phan* No. Doses Daily	Attacks
	Total Quan- tity	Sp. Gr.	Total Nitro- gen, Gm.	Uric Acid, Gm.	Creat- inin, Gm.	Creat- in as Creat- inin, Gm.	Uric Acid Mg. Per 100 Gm.		
32	1,120	1.01	6.57	6.261	0.51	0.07	....	0	
33	1,260	1.01	6.94	0.284	0.51	0	....	0	
34	1,060	1.01	6.44	0.284	0.49	0	....	0	
35	1,040	1.011	7.40	<b>0.28</b>	<b>0.51</b>	<b>0.05</b>	....	0	Moderate attack; rubbing relieved pain.
36	1,260	1.009	6.93	<b>0.27</b>	<b>0.51</b>	<b>0</b>	....	0	Moderate attack 8 a. m.
37	1,060	1.012	6.36	0.297	0.61	0	....	0	
38	1,140	1.012	6.80	0.29	0.60	0	....	0	
39	1,290	1.012	7.94	<b>0.29</b>	<b>0.54</b>	<b>0</b>	....	0	Slight in left wrist; disappears when rubbed.
40	1,180	1.011	7.32	<b>0.25</b>	<b>0.53</b>	<b>0.058</b>	....	0	Severe pain in both wrists in p. m.; swollen and red.
41	1,610	1.01	7.27	0.28	0.52	0	....	6	
42	1,460	1.011	7.36	0.58	0.51	0.09	....	6	
43	1,220	1.008	4.50	0.23	0.38	0.02	....	6	
44	1,380	1.012	6.72	0.23	0.60	0	....	6	
45	1,700	1.01	6.59	0.24	0.69	0	....	6	
46	1,400	1.012	7.20	<b>0.32</b>	<b>0.71</b>	<b>0</b>	<b>0.095</b>	6	Severe pain in both hands and wrists. Began in night and continued next day.
47	1,300	1.011	7.80	<b>0.32</b>	<b>0.73</b>	<b>0</b>	....	6	Attack somewhat less severe than on previous day.
48	690	1.013	6.03	<b>0.30</b>	<b>0.57</b>	<b>0</b>	....	6	Attack less severe than previous day.
49	780	1.013	5.40	0.27	0.50	0	....	6	
50	960	1.012	7.30	0.25	0.57	0	....	6	

\* Each dose 0.5 gm.

† Began 5 p. m.

towel, was sometimes used to increase the flow of blood; gentle massage of the forearm was also helpful in increasing the blood flow. Two samples of blood, approximately 20 gm. each, were collected for analysis. The oxalate was at once dissolved by shaking, and the blood and flask weighed.

The uric acid, creatinin and creatin in the urine were determined by Folin's methods, the nitrogen in the urine by Kjeldahl's method. The results are given in the accompanying tables.

## DISCUSSION OF THE RESULTS

*Uric Acid in the Blood.*—The amount of uric acid in the blood of Mrs. W. on day 2 was 2.10 mg. in 100 gm. (2.11 mg. in Sample A, and

2.09 mg. in B). This blood was taken during a period free from attack and before atophan had been administered. On day 17 blood was taken during an attack. This contained 2.02 mg. in 100 gm. (Sample A, 1.99 mg.; Sample B, 2.05 mg.). The uric acid in the blood of Mrs. L. was found to be 0.91 mg. per 100 gm. (Sample A, 0.87 mg.; Sample B, 0.94 mg.). From our own unpublished results and those of other investigators (Folin,<sup>4</sup> McLester,<sup>4</sup> Kocher<sup>5</sup>) we may assume that the normal amount of uric acid in the blood is about 2.00 mg. (0.5 to 2.9 mg.) in 100 gm. It should be observed that *in neither of our gouty patients was the uric acid content of the blood higher than that of normal individuals*. In one case it was distinctly low. Furthermore, *the amount of uric acid in the blood was the same during an acute attack as during a period free from attack*. Atophan (in 0.5 gm. doses six times a day) was administered from Day 2 to Day 14. The uric acid excretion increased, the amount of uric acid in the blood decreased to 0.66 mg. in 100 gm. (Sample A, 0.67 mg., Sample B, 0.65 mg.). These results following the use of atophan are comparable with those of other investigators. But notwithstanding the decreased content of the blood in uric acid there was a severe attack of gout on Day 7. These findings were confirmed by later findings. Atophan was given from Day 41 to Day 50. On Day 46 there was a severe attack followed by a less severe attack on two successive days. During the first day of atophan treatment the uric acid excretion was increased from 0.28 gm. to 0.58 gm. The amount in the blood fell to 0.95 mg. in 100 gm. of blood (Sample A, 0.94 mg.; Sample B, 0.95 mg.). In both of these cases it is important to emphasize that during atophan treatment we made analyses of the blood and urine; and the data show that the attacks came on *in spite of the fact that the uric acid content of the blood had been lowered* as a result of an artificial increase in the elimination.

*Effect of Attack on Elimination of Uric Acid.*—If the uric acid excretion (Mrs. W.) from Day 15 to Day 40, a period of twenty-five days when no atophan was being taken, is examined, it will be seen to be constant from day to day.<sup>6</sup> *During this period of twenty-five days with a constancy in the daily excretion of uric acid there were three attacks of gout*. In the case of Mrs. L. the uric acid likewise remained constant during the one attack (Day 21 and Day 22) which she suffered while under investigation.

4. McLester: THE ARCHIVES INT. MED., 1913, xii, 739.

5. Kocher: Deutsch. Arch. f. klin. Med., 1914, cxv, 380.

6. Except Days 21 and 22. The creatinin is so constant on these two days that one can hardly suspect any loss of specimen. The uric acid excretion for the two days taken together is 0.60, twice the usual amount for one day. A slight retention of uric acid on one day would explain the result.



It is difficult to see how the commonly accepted hypothesis of Gerrod that gout is due to the precipitation of uric acid from the blood supersaturated with this compound as a result of faulty excretion by the kidneys, or the related hypothesis that acute attacks of

TABLE 2.—URIC ACID, CREATININ, AND CREATIN EXCRETION OF A GOUTY PATIENT

Mrs. L., weight 43.2 kilos.

Day	Urine					Blood	
	Total Quantity	Sp. Gr.	Total Nitrogen, Gm.	Uric Acid, Gm.	Creatinin, Gm.	Creatin as Creatinin, Gm.	Uric Acid Mg. Per 100 Gm.
Preliminary							
1	800	1.011	6.52	0.289	0.58		
2	710	1.016	7.57	0.268	0.63		
3	580	1.022	8.38	0.289	0.69	....	0.51
4	840	1.018	8.48	0.32	0.67	0.38	
5	820	1.017	7.70	0.32	0.63	0.37	
6	660	1.02	7.96	0.34	0.64	0.36	
7	740	1.02	7.98	0.299	0.63	0.34	
8	660	1.023	7.92	0.446	0.98		
9	620	1.024	7.94	0.365	0.69		
10	660	1.024	7.96	0.332	0.68		
11	700	1.02	7.70	0.33	0.67		
12	900	1.016	7.94	0.328	0.66		
13	800	1.012	7.90	0.34	0.70		
14	720	1.022	8.12	0.354	0.70		
15	1,180	1.015	8.25	0.377	0.648		
16	1,290	1.02	7.86	0.35	0.61	0.14	Potassium citrate, 3 doses 4 gm. each.
17	840	1.02	7.52	0.33	0.66	0.31	Potassium citrate, 3 doses 4 gm. each.
18	1,200	1.012	7.44	0.297	0.56	0.14	Hydrochloric acid 0.5% solution, 3 doses 100 c.c. each.
19	1,480	1.012	8.34	0.31	0.66	0.15	Hydrochloric acid 0.5% solution, 3 doses 100 c.c. each.
20	1,090	1.014	7.97	0.32	0.78	0.09	Hydrochloric acid 0.5% solution, 3 doses 100 c.c. each.
21	600	1.016	7.89	0.34	0.78	0.18	Attack moderately severe.
22							Attack continued; much less severe in p. m.

gout are due to occasional increase of the uric acid content of the blood following intermittent impermeability of the kidney, can be harmonized with our findings.

Certain points of minor interest, which we hope to investigate further, are also to be noted:

1. Examination of the creatinin excretion of Mrs. W. from Day 18 to Day 40 shows that the creatinin excretion is not greatly affected during acute attacks of gout.

2. Atophan appears to affect the creatinin excretion. After administration (Mrs. W.) the *rise and fall* in the uric acid excretion is immediately followed by a *fall and rise* in the creatinin excretion (see Days 6 to 13 and Days 43 to 47); the creatinin excretion goes up as the uric acid goes down.

3. The creatinin excretion of one of our patients (Mrs. L.) was conspicuously irregular, varying from 0.58 gm. to 0.98 gm.

4. Creatin was occasionally present in small amounts in the urine of Mrs. W. and in large amounts in the urine of Mrs. L.

5. On Days 16 and 17, Mrs. L. was given moderately large quantities of alkali—sufficient to change the reaction of the urine from acidic to basic, and on Days 18 to 23 moderately large quantities of acid (for purposes unconnected with the present problem), with no effect in either case.

This disposes of the contention of Haig and others that alkali administration, by making the blood a better solvent for uric acid, leads to a sweeping out of increased quantities of uric acid in the blood, and that acid administration, by precipitating the uric acid from the blood into the tissues, decreases the uric acid excretion.

#### SUMMARY

The striking points in our data in two cases of gout are as follows:

1. There was no more uric acid in the blood than in blood of normal individuals.

2. The amount of uric acid in the blood was not altered during acute attacks of gout.

3. Uric acid excretion was not altered during acute attacks of gout.

4. Attacks of gout appeared during atophan administration, when, as shown by chemical analysis, the uric acid content of the blood had been greatly decreased.

In conclusion we wish to express our indebtedness to the members of the executive departments of the Robert B. Brigham Hospital, who have made this study possible.

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# STUDY XXIV: THE EFFECT OF THEOBROMIN SODIUM SALICYLATE IN ACUTE CHROMATE NEPHRITIS \*

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The effect of diuretics in acute nephritis has been the subject of much theorization and of some experimental work, especially during the past few years. The meager literature on the experimental work has been so recently reviewed by Fitz<sup>1</sup> in his article on the "Immediate Effect of Repeated Doses of Theobromin Sodium Salicylate and Theocin in Acute Experimental Nephritis" that it does not seem worth while repeating it here. In 1913 with Dr. Christian<sup>2</sup> I reported the results of our experiments on the effect of theobromin sodium salicylate on the duration of life of rabbits with acute uranium nephritis, and Walker and Dawson<sup>3</sup> reported in the same way the effects of theocin, caffeine, potassium acetate, spartein sulphate and water. More recently Dr. Christian<sup>4</sup> has reported the effect of theobromin sodium salicylate on renal function as measured by the excretion of phenol-sulphonaphthalein in acute uranium nephritis. It seemed, therefore, desirable to supplement this work of a year ago by making a study of the effect of this same diuretic in other types of acute experimental nephritis. Following the theories of Schlayer and his coworkers in the attempt to produce a vascular nephritis, arsenic acid was selected. After

\* Submitted for publication Jan. 9, 1915.

\* From the Laboratory of the Theory and Practice of Physic, Harvard Medical School.

\* This is one of a series of studies on experimental cardio-renal disease. Study I, Smith: *Boston Med and Surg. Jour.*, 1908, clyiii, 696; Study II, Christian: *Boston Med and Surg. Jour.*, 1908, clx, 8; Study III, Christian: *Jour. Am. Med. Assn.*, 1909, lii, 1792; Studies IV-VV, Christian, Smith and Walker: *THE ARCHIVES INT. MED.*, 1911, viii, 468-551; Study XVI, Christian and O'Hare: *THE ARCHIVES INT. MED.*, 1913, XI, 517; Studies XVII and XVIII, O'Hare: *THE ARCHIVES INT. MED.*, 1913, xii, 49, 61; Study XIX, Christian and O'Hare: *Jour. Med. Research*, 1913, xxviii, 227; Study XX, Walker and Dawson: *THE ARCHIVES INT. MED.*, 1913, xii, 171; Study XXI, Fitz: *THE ARCHIVES INT. MED.*, 1914, xiii, 945; Study XXII, Christian: *THE ARCHIVES INT. MED.*, 1914, xiv, 827; Study XXIII, Fitz: *THE ARCHIVES INT. MED.*, 1915, xv, 524.

\* This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

\* The theobromin sodium salicylate used was purchased under the trade name of Diuretin.

1. Fitz: *THE ARCHIVES INT. MED.*, 1914, xiii, 945.

2. Christian and O'Hare: *THE ARCHIVES INT. MED.*, 1913, xi, 517.

3. Walker and Dawson: *THE ARCHIVES INT. MED.*, 1913, xii, 171.

4. Christian: *THE ARCHIVES INT. MED.*, 1914, xiv, 827.

TABLE SHOWING EFFECT OF THEOBROMIN SODIUM SALICYLATE ON LIFE OF RABBITS WITH POTASSIUM BICHROMATE NEPHRITIS

	Rabbit No.	Weight gm.	Duration of Life After First Bichromate Injection (Days)	Average Life of Those that Died (Days)	Number Dead
<i>Series 1—</i>					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	846 862 864	2,100 2,060 2,260	6 4 17 *	5	2
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobromin sodium salicylate, daily; 0.014 gm. per kg.	866 865 877	2,250 2,100 2,060	3 6 7	5½	3
<i>Series 2—</i>					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	881 882 885	2,070 2,360 1,780	3 39 * 3	3	2
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobromin sodium salicylate, daily; 0.028 gm. per kg.	878 879 884	2,100 2,030 1,840	39 * 6 3	4½	2
<i>Series 3—</i>					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	883 886 889	1,900 2,230 2,060	7 25 * 25 *	7	1
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobromin sodium salicylate, daily; 0.056 gm. per kg.	888 890 891	2,050 2,230 2,080	3 5 25 *	4	2
<i>Series 4—</i>					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	893 894 895	1,790 2,020 2,730	21 27 * 26 *	21	1
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobromin sodium salicylate, daily; 0.56 gm. per kg.	896 901 902	2,350 2,040 1,880	19 18 27 *	18½	2

\* Experiment discontinued.

TABLE SHOWING EFFECT OF THEOBROMIN SODIUM SALICYLATE ON LIFE OF RABBITS WITH POTASSIUM BICHROMATE NEPHRITIS—(Continued)

	Rabbit No.	Weight gm.	Duration of Life After First Bichromate Injection (Days)	Average Life of Those that Died (Days)	Number Dead
Series 5—					
Potassium bichromate, 2 doses; 0.0175 gm. per kg.	899	2,500	5	5	1
	909	2,200	15 *		
	915	1,750	15 *		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.056 gm. per kg.	911	1,900	4	4½	3
	913	2,270	6		
	914	2,450	4		
Series 6					
Potassium bichromate, 2 doses; 0.0175 gm. per kg.	910	1,800	18 *	6	1
	917	2,000	18 *		
	923	2,100	6		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.014 gm. per kg.	916	1,850	18 *	5½	2
	921	1,950	7		
	920	2,050	4		
Series 7—					
Potassium bichromate, 2 doses; 0.0175 gm. per kg.	925	1,920	18 *	6	1
	930	2,820	18 *		
	924	1,800	6		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.028 gm. per kg.	926	2,450	2	3	2
	927	1,980	18 *		
	929	1,550	4		
Series 8—					
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Urea and salt daily	934	2,210	4	4	1
	949	2,000	10 *		
	952	1,940	10 *		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.028 gm. per kg. Urea and salt daily.	944	2,070	10 *	3	2
	947	2,240	2		
	951	2,110	4		

\* Experiment discontinued.

Average duration of life after first bichromate injection:  
 Bichromate only ..... 7 1/8 days  
 Bichromate and theobromin sodium salicylate..... 6 1/16 days  
 Number dead:  
 Bichromate only ..... 10  
 Bichromate and theobromin sodium salicylate..... 12

much work with this drug, however, I came to the same conclusion arrived at by Fitz and others working with it, that it was not possible to control the action of arsenic so as to produce regularly a uniform, workable nephritis, and so the plan of studying the effect of diuretics on a vascular type of nephritis was given up. For the study of a tubular type of nephritis potassium bichromate, which produces lesions confined almost exclusively to the tubules, was selected as the kidney irritant.

Forty-eight normal adult rabbits, on a known diet of carrot, oats and water, were divided into eight groups of six each. These, in turn, were subdivided into "controls," which received potassium bichromate only, and so-called "diuretic" rabbits which were given, in addition, theobromin sodium salicylate. The controls and diuretic animals were paired off in each group so as to be of approximately parallel weights.

The potassium bichromate was given subcutaneously on two successive days in body weight doses. The diuretic was given in a similar manner except that it was begun on the day of the second bichromate injection and was repeated daily until the animal died or until the experiment was discontinued. The dose of the two drugs was varied in each group so as to get the effect of different dosage of the diuretic in nephritides of varying degrees of severity. (For doses used, see table.)

In these eight groups observations were made on the comparative length of life of control and diuretic rabbits; their comparative pathology and their comparative water excretion. In a smaller number of these rabbits a comparative study was made on the output of phenol-sulphonaphthalein, nitrogen and sodium chlorid.

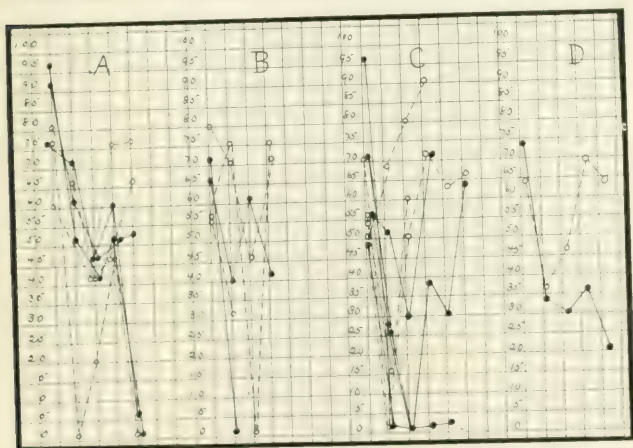
The primary object of the work was to determine whether or not theobromin sodium salicylate affected in any way the length of life of rabbits with acute chromate nephritis. Not all of the forty-eight rabbits died, but, as the table shows, of the twenty-eight that died only ten were controls, whereas eighteen, almost twice as many, had been treated with theobromin sodium salicylate. This is, I think, a rather striking result, more striking even than our results in uranium nephritis.

The average duration of life after the first dose of potassium bichromate was  $6\frac{1}{6}$  days for the diuretic rabbits, and  $7\frac{1}{8}$  for the controls. This too, though not so striking, is in favor of those not treated with the diuretic. These two results show rather conclusively that in this type of nephritis, as has already been shown for uranium nephritis, theobromin sodium salicylate is usually distinctly harmful. It must be said, however, that in Series 1 and 2, where small doses of bichromate and a small and medium dose, respectively, of theobromin sodium



salicylate were used, those diuretic animals that died lasted somewhat longer than the corresponding controls. This is in keeping with the results obtained previously in uranium nephritis, namely, that in mild types of nephritis small doses of theobromin sodium salicylate occasionally seem to prolong life.

No attempt was made to study the question of comparative pathology very accurately. Careful studies were made, however, of the kidneys of those rabbits that died, and the pathological picture of the controls was set off against that of the diuretic animals in the same



Dotted lines show excretion of phenolsulphonephthalein in rabbits which received potassium bichromate. Solid lines show phenolsulphonephthalein excretion in rabbits which received both potassium bichromate and theobromin sodium salicylate. *A* gives the results for rabbits 893, 894, 895, 896, 901 and 902; *B*, rabbits 924, 925, 930, 927 and 929; *C*, rabbits 931, 938, 933, 944, 939, 934, 949 and 952. (In the accompanying table is shown the dosage of drugs used and other details in regard to these rabbits.) In *D* is shown by the dotted line the average phenolsulphonephthalein excretion for all rabbits that received potassium bichromate but no diuretic, while by the solid line is shown the average excretion of those rabbits that received potassium bichromate followed by theobromin sodium salicylate.

group. This is scarcely a fair comparison. It was found, however, that the rabbits treated with the diuretic did seem to show slightly more pronounced tubular lesions.

The majority of the rabbits showed edema when examined post mortem; but, of those that did not, six were rabbits which had received the diuretic while three had not. As to the rest the amount of fluid was about the same in both divisions.

The question of change in the outflow of urine following the production of the nephritis was studied in carefully prepared intake and output charts. These showed on the whole that theobromin sodium salicylate not only did not produce any increase of water excretion, but seemed often to have caused an inhibition.

The phenolsulphonephthalein function test was performed in twenty-one animals. The results (see Chart A, B and C), though not at all uniform, show that the control rabbits (those that received the chromate but no diuretic) were less severely affected in the majority of cases, and that when they did get back to a normal output of phenolsulphonethalein they did so more quickly than the diuretic rabbits. This agrees with the results obtained by Dr. Christian. The harmful action of the diuretic drug is shown more clearly by charting the averages of the phenolsulphonephthalein output in the two groups of rabbits (see chart, D).

The nitrogen and sodium chlorid metabolism was studied in eight cases. No definite conclusions, of course, can be drawn from such a small number of cases, especially in view of the fact that the results are far from uniform. This last is true even when a fairly large amount of urea and salt was added to the daily diet to render the output more stable. Making three day averages of the output of the nitrogen and salt helps somewhat, but not greatly. The nitrogen output was measured by the Kjeldahl method, the sodium chlorid by Goodall's modification of the Volhard method. Charts of these eight cases show that in the diuretic rabbits there is usually a falling off rather than an increase in the nitrogen elimination immediately following the treatment with theobromin sodium salicylate. In the controls, on the other hand, there is, in some cases, an increase. As to the salt excretion the results are so variable that they indicate nothing.

#### CONCLUSIONS

In conclusion we may say that in an experimental tubular nephritis caused by potassium bichromate of a severe or moderately severe type theobromin sodium salicylate usually shortens the life of the animals; in mild cases it sometimes seems to prolong it.

On the whole, it seems to increase the lesion in the kidney and to hinder the excretion of water, phenolsulphonephthalein and possibly nitrogen.

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## CERTAIN ASPECTS OF BIOLOGICAL OXIDATION \*

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The subject of oxidation presents one of the most fascinating themes in the entire domain of chemistry. The various views which have been held regarding the nature of combustion and oxidation have always exercised a profound influence on chemical thought and on biological science and medicine. Modern views regarding the nature of oxidation date from the work of Lavoisier, who observed that, in the process of oxidation, oxygen adds itself to the substance oxidized, and that the resulting one or more products weigh more than the original material by exactly the weight of oxygen required to effect the oxidation.

It is not within the scope of this lecture to recount the views which have been held regarding the mechanism of oxidation in general. It would also be quite futile to review the whole subject of vital oxidation in the time at our disposal. I shall therefore confine my remarks to a small part of the field in which I have been particularly interested for several years.

The subject of vital oxidation may be divided into the following phases:

1. The mechanism by which oxidative processes are brought about in living material.
2. The nature of the substances oxidized by living organisms.
3. The relation between oxidation within the body and the energy requirements of the organism.
4. The relation of oxidative processes to other chemical processes in the body.
5. The effect of various substances and of various conditions on vital oxidation.
6. The relation of vital oxidation to functional activity.

Notwithstanding the great interest connected with the first four phases of oxidation here enumerated, I shall have very little to say regarding them except as they bear directly on the last two phases.

It was recognized by Lavoisier that oxidation is constantly occurring in the body, and it was surmised that the body derives its heat from oxidation. Ever since the establishment of the principle of

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\* Lecture read before the Harvey Society, New York, Nov. 8, 1914.

the conservation of energy, the body has been regarded as an engine which converts the latent chemical energy of foodstuffs by oxidation into heat, mechanical work and all the manifestations of life. Oxidation within the body was looked on for many years as quite similar to combustion outside the body. It is perfectly evident, however, that great differences exist between oxidation within and without the organism. Thus proteins, carbohydrates and fats are oxidized within the body at a temperature of  $37^{\circ}$  C., whereas it requires a far higher temperature to oxidize these substances in the air. In the attempts to explain this fact, the group of oxidizing enzymes, or oxidases, was discovered. Much work has been done to indicate the great differences between oxidation within and without the body. It has been shown that many substances which are readily oxidized outside the body are either very incompletely oxidized or not oxidized at all within the organism. Under this list may be classed carbon monoxid, oxalic acid, and many others. The selective oxidation of many organic substances in the body is another very remarkable characteristic of vital oxidation. Thus very slight changes in the structure of a substance may completely prevent its oxidation in the body. A great deal of work has been done on the relation of chemical constitution to the property of undergoing oxidation in the organism. I shall take occasion later to refer to another remarkable difference between oxidation within and without the body.

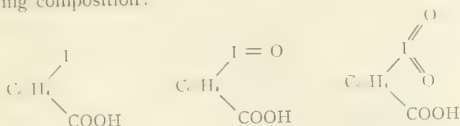
In 1901 Kastle and <sup>1</sup> showed that certain of the organic peroxids give practically all of the reactions of certain oxidases widely distributed in living matter. We found, for instance, that benzoyl peroxid gives the well-known guaiacum reaction, and that the bluing of guaiacum by benzoyl peroxid can be inhibited by hydrocyanic acid in the same manner that this substance inhibits the bluing of guaiacum by the oxidases. On the basis of this work and on the presumption that the oxidases play a rôle in pathological as well as physiological processes, I was led to study the pharmacological action of benzoyl peroxid and also any therapeutic uses to which it might be put.<sup>2</sup> The substance proved to be markedly antiseptic and extremely useful in the treatment of local infection; in fact, its effect in local infection was so remarkable as to suggest that its beneficial effect could not be attributed entirely to its antiseptic action. This naturally suggested that the active oxygen contained in benzoyl peroxid had some peculiar effect on the tissues, increasing their resistance to infection. The nature of this increased resistance was not determined at that time. I shall refer to this again later. Benzoyl peroxid is but slightly soluble in water, so that its effect

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1. Kastle and Loevenhart: *Am. Chem. Jour.*, 1901, xxvi, 539.

2. Loevenhart: *Therap. Monatsch.*, 1905, p. 426.

on general infections could not be studied. In casting about for a substance soluble in water which might contain oxygen in a physiologically available form, and which could be injected intravenously, it was decided to make a careful pharmacological study of the sodium salts of iodbenzoic, iodosobenzoic and iodoxybenzoic acids. These acids, which were first prepared by Victor Meyer and his co-workers,<sup>3</sup> have the following composition:



Iodbenzoic acid contains no active oxygen. Iodosobenzoic acid contains 6.06 per cent. of active oxygen. Iodoxybenzoic acid contains 11.43 per cent. of active oxygen. By active oxygen I mean oxygen which in the chemical sense is very active outside the body and which in the compounds under consideration is the oxygen bound to the iodine.

Grove and I<sup>4</sup> sought to determine whether the oxygen contained in these substances is physiologically available, that is to say, whether the oxygen bound to iodine in these substances can be utilized by the organism for purposes of physiological oxidation. We found that the sodium salts of iodosobenzoic and iodoxybenzoic acids instantly oxidize hemoglobin to oxyhemoglobin. We found that sodium iodosobenzoate can furnish the oxygen for at least one peroxidase reaction. It was found that while neither blood nor sodium iodosobenzoate is capable of oxidizing phenolphthalein to phenolphthalein, together they are capable of effecting this oxidation. Dilute solutions of sodium iodosobenzoate and sodium iodoxybenzoate taste very much like solutions of hydrogen peroxide. All of these facts indicate that the oxygen which they contain is physiologically available.

Arkin showed that sodium iodosobenzoate and sodium iodoxybenzoate are from one hundred to two hundred times as highly bactericidal as sodium iodbenzoate on *Bacillus typhosus*.<sup>5</sup> This difference can be attributed only to the oxidizing action of the former substances. On intravenous injection it was found that sodium iodosobenzoate and iodoxybenzoate markedly depress the respiratory and vasomotor centers, whereas the iodbenzoate has no such effect. Therefore, the effects of the two former substances on these centers must be attributed to the physiologically active oxygen which they contain. It would thus appear

3. Meyer, Victor: Ber. d. deutsch. chem. Gesellsch., 1892, xxv, 2632; 1893, xxvi, 1354, 1727; 1894, xxvii, 1600.

4. Grove and Loevenhart: Jour. Pharmacol. and exper. Therap., 1911, iii, 101.

5. Arkin: Jour. Pharmacol. and exper. Therap., 1911, iii, 145.

that a substance which apparently increases oxidation within the respiratory and vasomotor centers, depresses them. It has been known for a long time that hydrocyanic acid is one of the most powerful stimulants of the respiratory center. It is also well known that hydrocyanic acid depresses vital oxidation. Therefore it seemed interesting to determine whether an antagonism existed between the action of hydrocyanic acid and iodosobenzoate. In order to determine this, cannulas were placed in both femoral veins of a cat. In the left femoral vein a solution of sodium iodosobenzoate was injected and its effect determined. After a short time sodium cyanid was injected into the right femoral vein, in order to determine the effect of a given dose in the animal under experimentation. Then both substances were injected simultaneously into the opposite veins. The complete antagonism of the two substances in their action on the respiratory center was readily seen.<sup>6</sup> This further indicated that iodosobenzoate increased oxidation in the center, since it was capable of antagonizing a substance known to inhibit vital oxidation.

Eyster and I<sup>7</sup> showed that sodium iodosobenzoate, when perfused through the isolated mammalian heart, has a marked effect on the size of the beat even in very dilute solutions, whereas iodbenzoate has very much less action. We found that most of the active oxygen of the iodosobenzoate is removed from the solution on perfusing through the heart, and that the more vigorously the heart is beating the greater is the amount of oxygen taken up by the heart from this compound. Although iodoxybenzoate is apparently as active on the respiratory center as iodosobenzoate, it is much less active in altering the activity of the isolated heart. The heart also takes up far less oxygen from a solution of iodoxybenzoate than from iodosobenzoate, which again clearly indicates that it is the active oxygen in these compounds which accounts for their pharmacological action. It is also very interesting as showing how futile it is to predict, from knowledge previously gained with one tissue, what effect a given oxidizing substance will have on another tissue. In fact, the longer one works at the problems of vital oxidation, the less willing he becomes to make predictions. The effect of any new factor or condition cannot be foretold. It must be ascertained by experiment.

The action of iodoso- and iodoxybenzoate on the circulation and respiration seemed so interesting that we determined to step aside from the original object of the investigation, namely, the quest of a substance for the treatment of general infection, long enough to determine the relation between physiological activity and changes in the rate of

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6. Grove and Loevenhart: *Jour. Pharmacol. and exper. Therap.*, 1911, iii, 131.

7. Eyster and Loevenhart: *Jour. Pharmacol. and exper. Therap.*, 1913, v, 21.



oxidative processes. Strange to say, this question had never been carefully attacked as such, and the knowledge on the subject, which was more or less desultory, did not elucidate the problem satisfactorily. The reaction of the animal to asphyxia has been investigated for the last sixty years. Asphyxia is, however, a complicated condition. There exists both a lack of oxygen and an excess of carbon dioxid, and the relative parts played by these two factors in producing the symptoms of asphyxia have been the source of endless controversy. Furthermore, products of incomplete oxidation having an acid character arise during asphyxia, and to these the symptoms of asphyxia have also been ascribed in part. The striking symptoms of asphyxia, however produced, are the following: increase in the rate and depth of the respiration, rise of blood pressure, slowing of the pulse, cessation of respiration, general convulsions followed by paralysis, marked and progressive fall of blood pressure, death.

I cannot review the previous work on the subject of asphyxia, and must confine myself to recounting certain experiments which seem to us to demonstrate conclusively that the symptoms of asphyxia can be brought about by decreased oxidation. Gasser and I<sup>8</sup> produced decreased oxidation by methods which did not permit of any accumulation of carbon dioxid or of acid products in two ways:

1. By injecting sodium cyanid intravenously.
2. By injecting pure carbon monoxid into the trachea without interfering with the respiration in any way.

Artificial respiration was given when the natural respiration was depressed, thus preventing the accumulation of carbon dioxid. In the rabbit the injection of sodium cyanid into the jugular vein stimulates the respiratory center, on the average, within three to four seconds. Stewart<sup>9</sup> found that it requires 2.8 seconds for the blood to pass from the left jugular vein to the right carotid in the rabbit. Thus the latent period of stimulation of the respiratory center by sodium cyanid is practically the time required for the substance to reach the center. This extremely rapid action precludes all possibility of explaining the stimulation as due to excess of carbon dioxid or the accumulation of acid products. It proves beyond peradventure that the cells respond with stimulation to a decrease in their own oxidative processes directly. Similarly, the vasomotor and cardio-inhibitory centers are stimulated, but the latent period is longer than in the case of the respiratory center. The order of stimulation is, first, respiratory center, second, the vasomotor center and last, the cardio-inhibitory center. With carbon monoxid quite similar results were obtained, but a little longer time was

8. Gasser and Loevenhart: *Jour. Pharmacol. and exper. Therap.*, 1914, v, 239.

9. Stewart: *Jour. of Physiol.*, 1894, xv, 4.

required. Here the stimulation of the respiratory center occurs within six and one-half seconds. The extra time required to produce stimulation by carbon monoxid can readily be accounted for by the time required for the gas to be drawn into the lungs and pass through the endothelium into the blood. The difference between the action of carbon monoxid and hydrocyanic acid in these reactions is this: The carbon monoxid by combining with hemoglobin and forming carbon monoxid hemoglobin reduces the amount of oxygen which the cells receive, whereas hydrocyanic acid does not interfere with the supply of oxygen, but interferes with the consumption of oxygen by the tissues through its inhibiting action on the oxidases. This fact illustrates that *decreased oxidation may occur when the supply of oxygen is not diminished and that the term decreased oxidation is not synonymous with oxygen want. Oxygen want is but one means of producing decreased oxidation.* Every phase of the pharmacologic action of hydrocyanic acid and carbon monoxid can be explained on this basis. These results clearly prove that decreased oxidation leads first to increased functional activity or stimulation and later to depression.

The effect of reducing oxidation in these centers depends on three factors: first, on the extent to which the oxidative processes are reduced; second, the suddenness with which they are reduced; third, the condition of the centers.<sup>10</sup> If oxidation is reduced below a certain level, stimulation will not be observed. The more suddenly the rate of oxidation is reduced, the greater will be the stimulation. If the reduction of the rate of oxidation is very slow no stage of stimulation will be noted, as the irritability of the cells will then decrease faster than the stimulus increases. Finally, the better the condition of the center the more readily is the stage of stimulation demonstrable and conversely, the poorer the condition of the center the more difficult it is to elicit a stage of stimulation. To summarize, then, we have found that a depression in the rate of oxidative processes in the medullary centers leads primarily to stimulation, whereas our work on iodosobenzoate and iodoxybenzoate showed that an increase in the rate of oxidative processes causes decreased activity or depression. In other words, the functional activity varies inversely with changes in the rate of oxidative processes. We<sup>11</sup> have attempted to form some conception which would account for this inverse relationship between functional activity and changes in the rate of oxygen utilization by the cell. Verzář,<sup>12</sup> working on the gaseous metabolism of muscle, and Barcroft and Piper<sup>13</sup> on the

10. Loevenhart: Arch. f. d. ges. Physiol. (Pflüger's), 1913, cl, 379.

11. Gasser and Loevenhart: Jour. of Pharmacol. and exper. Therap., 1914, v, 239.

12. Verzář: Jour. Physiol., 1912, xliv, 243.

13. Barcroft and Piper: Jour. of Physiol., 1912, xliv, 359.

gaseous metabolism of the submaxillary gland, have shown that the period of increased utilization of oxygen outlasts by several minutes the period of increased functional activity following stimulation. Barcroft and Piper found that following certain forms of stimulation, maximum utilization of oxygen occurs when the saliva almost ceased to flow. They say: "Probably therefore gland, like muscle, is a mechanism in which oxidation serves to replenish a store of potential energy which is liberated in the act of secretion." It would seem that we have two sets of processes going on within cells, one of which requires the acquisition of oxygen from without the cell. Since the cell continues to fix oxygen at a greatly increased rate for a time after functional activity has ceased and since heat continues to be liberated after the contraction of a muscle as shown by A. V. Hill<sup>14</sup> it would seem that the fixation of oxygen by the cell must be the beginning of a series of oxidations. Let us designate this phase of oxidation within the cell as the R processes, since R will suggest rest and recovery. The essential feature of the R processes is that they require oxygen from without the cell. From our point of view functional activity is the external manifestation of a set of chemical reactions occurring within the cell. Since energy is liberated during functional activity we must assume that these processes are also oxidative at least in part. Let us designate the processes of which function is the external expression as A processes, since A will suggest activity. We conceive that neither the A nor the R processes are ever in complete abeyance during life but that their relative intensity determines the relative state of activity of the cell.

The work with iodosobenzoate and iodoxybenzoate indicates that a stimulation of the R processes (oxygen fixation) retards the A processes and depression results. On the other hand, if the R processes are depressed, as by the use of carbon monoxid or sodium cyanid, it would seem that the cell must derive its energy from the A processes and increased functional activity must result. This is the only conception we have been able to form to account for the reciprocal relationship of oxygen fixation and functional activity. We know that an increase in the A processes entails an increase in the R processes, but since the latter outlast the former it would appear that the R processes lag behind. Since recuperation apparently does not occur under anesthesia, it would follow that both the A and the R processes are depressed in this state. Our work indicates also that when the R processes fall below a certain level, all functional activity ceases, or, in other words, the A processes cease. According to our point of view, the stimulating action of carbon dioxid is due to its power to depress the R processes

14. Hill, A. V.: Jour. Physiol., 1913, xlvii, 28.

just as hydrocyanic acid does. We believe that under physiological conditions the oxidative processes and therefore the functional activity of the respiratory center are conditioned by the carbon dioxid tension and not by the oxygen tension. This follows from the work of Haldane and his co-workers.

We have recently turned our attention to another phase of the proposition that decreased oxidation primarily stimulates cells. The previous work showed that the cells of the respiratory center are apparently more sensitive to alteration in the rate of their oxidative processes than any cells in the body, and respond most readily with stimulation to a decrease in their oxidative processes. This is what we should expect, since the respiratory center, by controlling the entrance of oxygen into the body and the exit of carbon dioxid, really controls one of the fundamental conditions for tissue oxidation. From the lungs to the tissues the oxygen must be carried by the hemoglobin. Since the red blood corpuscles and hemoglobin are produced by the red bone-marrow, it is obvious that the red bone-marrow supplements the action of the respiratory center in supplying the tissues with oxygen.

Paul Bert<sup>15</sup> thirty-six years ago showed that the oxygen carrying power of the blood increases at high altitudes. He explained this as due to a reaction of the organism to accommodate itself to the decreased pressure of oxygen in the atmosphere. The facts brought out by Bert as well as his explanation of the blood changes have been the subject of much controversy. The majority of investigators, however, have agreed with Bert that there is an increase in erythrocytes and hemoglobin at high altitude. I cannot review the views which have been held regarding these phenomena, but will merely enumerate some of them. 1. The increase is insignificant. 2. The erythrocytes and hemoglobin always increase proportionately and the increase is due to concentration of the blood either by loss of water from the body through evaporation or by the passage of plasma from the blood to the tissues. Again, the blood changes have been attributed to various physical factors such as (1) a displacement of the diaphragm upward and an alteration in the pulmonary circulation, (2) lessened vital capacity of the lungs at reduced pressure, etc. There are obviously many factors which may play a rôle in the effect of reduced atmospheric pressure on the blood. From our point of view, the increase in the hemoglobin and red blood corpuscles is probably due to a stimulation of the bone-marrow by decreased oxidation within the bone-marrow itself.

I should like to describe briefly the apparatus which Mr. A. C. Kolls and I have devised in order to attack this problem.<sup>16</sup> This apparatus

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15. Bert, Paul: *La pression barométrique*, 1878, p. 1108; *Compt. rend. Acad.*, 1882, xciv, 805.

16. A description of this apparatus will soon be published.

was devised for the purpose of keeping animals in an atmosphere of reduced oxygen tension and at the same time to maintain them at the normal atmospheric pressure and thereby exclude all of the physical factors of high altitude. It consists of a respiratory chamber, the air of which is kept at a constant composition. The arrangement for absorbing carbon dioxid and water which the animal produces is that devised by Professor Benedict,<sup>17</sup> and the oxygen supply is automatically controlled by a mechanism quite similar to that used in Professor Lusk's laboratory and described by Williams.<sup>18</sup> We have introduced certain modifications which greatly facilitate the work that we have in hand. The results which Mr. H. C. Dallwig, Mr. A. C. Kolls and I have obtained with this apparatus may be indicated by citing two or three experiments out of a large number.<sup>19</sup>

## I. REDUCED OXYGEN EXPERIMENT

*Rabbits 4 and 5*

Length of experiment.....	132 hours
Average oxygen tension.....	11.98 per cent.
Average carbon dioxid.....	0.08 per cent.
Average per cent. humidity....	{ Inside 33 per cent. { Outside 33 per cent.

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 4—Before experiment.....	13.98	6,678,000
After 132 hours.....	16.97 (+ 21.4)	8,417,000 (+ 26)
No. 5—Before experiment.....	14.39	8,384,000
After 132 hours.....	17.43 (+ 21 )	8,490,000 (+ 1.3)

## II. CONTROL EXPERIMENT

*Rabbits 9, 10 and 11*

Length of experiment.....	167.5 hours
Average oxygen tension.....	20.9 per cent.
Average carbon dioxid tension.....	0.21 per cent.

## Weight

No. 9 (albino) Before control	852 gm.	After	970 gm. (+ 118 gm.)
No. 10 (albino) Before control	861 gm.	After	935 gm. (+ 74 gm.)
No. 11 (albino) Before control	790 gm.	After	898 gm. (+108 gm.)

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 9—Before control .....	10.9	5,293,000
After control .....	11.58 (+ 6.2)	5,772,000 (+ 9 )
No. 10—Before control .....	13.1	6,389,000
After control .....	13.74 (+ 4.9)	6,512,000 (+ 1.9)
No. 11—Before control .....	12.66	6,152,000
After control .....	11.54 (— 8.8)	5,827,000 (— 5.3)

17. Benedict: Deutsch. Arch. f. klin. Med., 1912, cvii, 156.

18. Williams: Jour. Biol. Chem., 1912, xii, 317.

19. A complete account of these experiments will soon be published.

## III. REDUCED OXYGEN EXPERIMENT

*Rabbits 9, 10 and 11*

Length of experiment.....147 hours  
 Average oxygen tension .....10.98 per cent.  
 Average carbon dioxid tension..... 0.19 per cent.

## Weight

No. 9—Before experiment 970 gm. After 1,060 gm. (+ 90 gm.)  
 No. 10—Before experiment 935 gm. After 1,070 gm. (+ 135 gm.)  
 No. 11—Before experiment 898 gm. After 973 gm. (+ 75 gm.)

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 9—Before experiment .....	11.58	5,772,000
After experiment .....	15.68 (+ 35.4)	7,544,000 (+ 30.7)
2 days after .....	16.70 (+ 44.2)	7,707,000 (+ 33.5)
10 days after .....	15.26 (+ 31.8)	7,442,000 (+ 28.9)
23 days after .....	11.8 (+ 1.9)	6,000,000 (+ 3.9)
No. 10—Before experiment .....	13.74	6,512,000
After experiment .....	16.38 (+ 19.2)	7,301,000 (+ 12.1)
2 days after .....	15.82 (+ 15.1)	7,186,000 (+ 10.3)
10 days after .....	16.76 (+ 22 )	7,635,000 (+ 17.2)
23 days after .....	15.77 (+ 14.8)	7,533,000 (+ 15.7)
No. 11—Before experiment .....	11.54	5,827,000
After experiment .....	17.02 (+ 47.5)	7,266,000 (+ 24.7)
2 days after .....	14.70 (+ 27.4)	7,200,000 (+ 23.6)
10 days after .....	14.83 (+ 28.5)	6,918,000 (+ 18.7)
23 days after .....	14.47 (+ 25.4)	6,872,000 (+ 17.9)

## IV. REDUCED OXYGEN EXPERIMENT

*Rabbits 15 and 16*

Length of experiment.....260.5 hours  
 Average oxygen tension .....10.6 per cent.  
 Average carbon dioxid tension..... 0.2 per cent.

## Weight

No. 15—(Gray and white)—  
 Before experiment, 1,050 gm. After 1,130 gm. (+ 80 gm.)  
 No. 16—(Albino)—  
 Before experiment, 1,010 gm. After 1,150 gm. (+ 140 gm.)

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 15—Before experiment .....	10.6	5,376,000
3 days' run .....	13.32 (+ 25.7)	5,920,000 (+ 10.10)
6 days' run .....	16.76 (+ 58.1)	6,620,000 (+ 23.1 )
11 days' run .....	15.92 (+ 50.2)	5,715,000 (+ 6.3 )
No. 16—Before experiment .....	11.16	5,952,000
3 days' run .....	12.28 (+ 10 )	6,075,000 (+ 2.1 )
6 days' run .....	14.96 (+ 34 )	7,018,000 (+ 17.9 )
11 days' run .....	15.26 (+ 36.7)	6,850,000 (+ 15.1 )

We have obtained many equally striking increases in other experiments. It is noteworthy that in Rabbit 5 the large increase in hemoglobin was not accompanied by a decided increase in the red blood cor-



puscles, showing clearly that the results could not be due to increased concentration of the blood, in which case the red blood corpuscles and hemoglobin would have increased proportionately. Blood smears stained with Jenner stain showed a large number of basophilic macrocytes. The blood smear also left no doubt that we were here dealing with a stimulation of the bone marrow. The animals which we have used fall into four groups:

1. Those which show an increase in both the hemoglobin and red blood corpuscles.
2. Those which show an increase in the hemoglobin without an increase in the corpuscles.
3. Those showing an increase in the corpuscles with no change in the hemoglobin.
4. Those showing little or no increase in either the red corpuscles or hemoglobin. The percentage of refractory animals (Group 4) is quite small.

An increase in the carbon dioxid in the atmosphere of the chamber with the normal oxygen concentration produces relatively little effect on the blood count in comparison with atmospheres poor in oxygen. We have some indication, however, that increased carbon dioxid here, as in the case of the respiratory center may stimulate the bone-marrow. In the case of the bone-marrow, however, the stimulation is slight whereas it acts powerfully on the respiratory center. It is interesting then that the respiratory center and the bone-marrow conduct themselves alike with regard to alteration in their own oxidative processes, since these two tissues provide the primary conditions for tissue oxidation. The work is interesting further in connection with polycythemia as observed clinically. It would seem that we might expect to find polycythemia in any chronic respiratory or circulatory condition which would result in the bone-marrow's receiving an insufficient supply of oxygen. In some of our experiments we have allowed animals to remain in the box at the normal oxygen concentration, and under these conditions, no increase in the red blood corpuscles and hemoglobin was noted. We have made certain observations in the box on the oxygen concentration required for a continuance of life, and compared with this the oxygen concentration required to support the flame of various combustible materials. It was shown by Clowes<sup>20</sup> that various combustible gases and liquids would burn only at definite minimum oxygen concentrations. We have confirmed certain phases of Clowes' work. Alcohol ceases to burn when the oxygen concentration falls to 15 per cent. The Madison illuminating gas ceases to burn in an oxygen con-

20. Clowes and Redwood: *Proc. Royal Soc. London*, 1894, lvi, 2.

centration of about 13 per cent. At about this point a flaming pledget of cotton saturated with ether is extinguished. The hydrogen flame is extinguished at about 6.6 per cent. oxygen. Below this point no combustible substances which we have studied will produce a flame. Animals continue to live, however, in an oxygen concentration far below this point. Thus we have found it necessary in order to produce alarming symptoms and death in rabbits to reduce the oxygen to between 3 and 3.5 per cent. This brings out one of the most striking differences between vital oxidation and ordinary combustion. If the atmosphere of the earth should become altered so as to contain only one-half the amount of oxygen, animal life would not be interfered with in any way, but it would be impossible to run a locomotive or to burn illuminating gas, and many of the substances which we consider dangerously inflammable would be as non-inflammable as water.

To return for a moment, before closing, to the original subject of the effect of physiologically active oxygen on inflammation and on immunity processes, I should like to refer briefly to two pieces of work. Prof. L. Hektoen<sup>21</sup> has investigated the effect of iodosobenzoate and iodoxybenzoate on certain immunity reactions. He injected these substances intravenously in dogs and found that they greatly increase the production of specific hemolysin following a single injection of 10 per cent. suspension of goat blood. The results were striking. The increase in hemolysin in the animals receiving the treatment was from 12 to 60 times as great as in the control animals. Iodbenzoate without active oxygen is without effect. Whether physiologically active oxygen will similarly stimulate the production of other immune bodies remains to be determined by further experiment. It is sufficiently obvious that if we could similarly increase the production of diphtheria antitoxin, it would be of great value.

Dr. S. Amberg and his co-workers<sup>22</sup> in a series of investigations have shown that iodosobenzoate and iodoxybenzoate injected intravenously or intraperitoneally have the power of markedly inhibiting the local inflammatory reaction as produced by mustard oil or bacterial toxins injected intracutaneously or instilled into the conjunctival sac, whereas iodbenzoate, possessing no physiologically active oxygen, is entirely without effect. The results are very striking indeed.

Many attempts of an unscientific character have been made to use oxygen in some form such as ozone, compressed air, etc., in the treatment of disease. I need only refer to the extensive and disastrous use of potassium chlorate internally which was in vogue for many years.

21. Hektoen, L.: *Tr. Chicago Pathological Soc.*, 1911, viii, 138.

22. *Jour. Pharmacol. and exper. Therap.*, 1912, iii, 223; *Jour. Am. Med. Assn.*, 1912, lix, 1598; *Ztschr. f. d. ges. exper. Med.*, 1913, ii, 19, and oral communication.

It was supposed that since it is a very strong oxidizing agent outside the body that it would facilitate oxidation within the organism. This substance, however, does not lose its oxygen in the body, but is excreted unchanged in the urine. Dr. Abraham Jacobi<sup>23</sup> pointed out the great danger attendant on its use internally. The investigations which I have reviewed indicate that at some future time we may find important therapeutic applications of the results of studies in vital oxidation, but we hope that the next attempt will be founded on a basis of fact and will be subjected to careful scientific scrutiny before it is given to the profession.

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23. Jacobi, Abraham: Tr. Med. Soc., New York, 1879, p. 365.

## UROBILIN IN THE STOOL—AN INDEX TO BLOOD DESTRUCTION \*

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This work was undertaken with the idea of determining whether the quantitative estimation of urobilin in the stool can be relied on to indicate the degree of blood destruction going on in the body, and also whether such estimation is of practical clinical value.

According to the theory most commonly accepted, urobilin is a decomposition product of bile, formed chiefly in the intestine by the action of putrefactive bacteria on the bile pigments. The quantity of urobilin in the feces does not represent the total amount of bile excreted into the intestine, for part of the urobilin is reabsorbed in the form of urobilinogen. Yet there seems to be a pretty constant relationship between the two, and the urobilin output may be taken as a rough measure of bile excretion. Since the amount of bile formed is, with a normal liver, directly dependent on the quantity of blood pigment brought to it, the variations in urobilin excretion may therefore be considered to indicate corresponding fluctuations in the amount of blood being destroyed.

The few investigators who have contributed to this subject are practically agreed in their results. Both Eppinger and Charnas<sup>1</sup> and Wilbur and Addis<sup>2</sup> state without reservation that an increased quantity of urobilin in the stool signifies an increased blood destruction. Simpson<sup>3</sup> who made many estimations on the stools of malaria patients, agrees with the above authors, and finds that the amount of urobilin excreted runs parallel with the intensity of hemolysis occurring during the course of the disease.

The method used was that employed by Wilbur and Addis,<sup>2</sup> which was found to be satisfactory and not too time-consuming. Briefly, the procedure consists in collecting the total twenty-four hourly amount of stool, protected from the light, emulsifying it in water, extracting a portion of this in a mechanical shaker with acid alcohol, next adding zinc acetate and Ehrlich's reagent, which bring out the spectroscopic

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\* This work was carried on under a Dalton scholarship.

\* From the Pathological Laboratory and the West Medical Service of the Massachusetts General Hospital.

1. Eppinger and Charnas: *Arch. f. klin. Med.*, 1913, lxxviii, 387.

2. Wilbur and Addis: *THE ARCHIVES INT. MED.*, 1914, xiii, 235.

3. Simpson: *Biochem. Jour.*, 1911, p. 378.

absorption bands of urobilin and urobilinogen, respectively. The solution is then diluted progressively till these absorption bands disappear and the reading made at this point. Thus the estimation, in terms of dilutions of the total twenty-four hourly stool, is really relatively quantitative.

As the daily variations in the urobilin output are often great, the following estimations represent an average of at least six days stools with very few exceptions, and often ten days or more. The normal excretion was determined in six individuals, four convalescent patients in whom there was no reason to expect abnormal blood destruction, and two normal persons. These varied from 2,000 to 8,500 dilutions. In none of the cases studied since, with a normal hemoglobin metabolism, has the urobilin reached 9,000. This figure, therefore, has been taken as the upper limit of normal average elimination. The normal given by Wilbur and Addis is practically identical with this.

Charnas used a very complicated and time-consuming method for extracting the urobilinogen from the stool and determining its amount by weight. The normal output in his cases averaged 0.13 gm. which would correspond approximately to 5,000 dilutions, the average normal in this series. On account of the instability of both urobilin and urobilinogen, and the difficulty of separating these substances out in pure form, no attempt is made here to translate dilutions into terms of weight.

*Pernicious Anemia.*—The eleven cases of group "A" all showed marked clinical evidence of increased blood destruction. In ten, the red count and hemoglobin were falling, and the eleventh remained about stationary. None were of the aplastic type. The highest readings were given by the four sickest patients, three of whom died. In striking contrast to these are the two cases of pernicious anemia in group "B" which were undergoing a rather rapid remission; the normal urobilin output during this phase of the disease being quite in harmony with the cessation of abnormal hemolytic activity.\* This observation has also been made by Addis.<sup>4</sup>

*Malaria.*—The case of malaria was in an acute attack with a hemoglobin of 50 per cent.

*Congenital Hemolytic Jaundice.*—A very high urobilin excretion might well be expected in a hemolytic process severe enough to produce jaundice. Despite the evidence of great hemolysis, grave anemia rarely appears in this disease. This seems to suggest that in pernicious

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\* Urobilin in pernicious anemia as influenced by splenectomy, transfusion and salvarsan will be reported in a separate paper.

4. Addis: THE ARCHIVES INT. MED., 1915, xiv, 413.

anemia there is another factor besides hemolysis; perhaps a weak marrow function. This case gave the highest estimation of the series, agreeing with the results of two reported cases of Eppinger and Charnas.

TABLE OF CASES

A. CASES SHOWING AN INCREASE OVER NORMAL		No. of Cases	Urobilin
1. Pernicious anemia .....	11		
Highest .....			30,000
Lowest .....			10,800
Average .....			21,800
2. Malaria .....	1		22,300
3. Congenital hemolytic jaundice .....	1		64,800
4. Secondary anemia—carcinoma (Regenerative type of blood) .....	1		22,000
B. CASES WITHIN NORMAL LIMITS			
1. Pernicious anemia .....	2	a)	3,600
(Undergoing remission) .....		b)	2,600
2. Secondary anemia .....	6		
a. Bleeding hemorrhoids .....			5,900
b. Carcinoma of prostate .....			7,400
c. Carcinoma of stomach .....			2,900
d. Endocarditis .....			4,800
e. Tuberculosis .....			5,000
f. Septicemia .....			4,100
3. Grave anemia—questionably pernicious or early leukemia .....	1		7,600
4. Leukemia .....	3		
a. Myelogenous .....			5,600
b. Myelogenous .....			6,400
c. Lymphatic .....			5,500
5. Biliary cirrhosis—jaundice .....	2		
a. Infectious type .....			2,700
b. Splenic (anemia?) type .....			6,000
6. Banti's Disease .....	1		2,800
7. Chronic passive congestion .....	2	a)	3,900
		b)	7,200
8. Pneumonia—jaundice .....	2	a)	8,800
		b)	3,300
9. Post-transfusion toxemia—jaundice. (Hemophilia) .....	1		1,400
10. Paroxysmal hemoglobinuria .....	1		4,200
11. Gastric ulcer—tarry stools .....	1		2,400

*Secondary Anemia.*—The one case of secondary anemia in group "A"—carcinoma of the stomach—had a large spleen and a blood which although compatible with a severe secondary anemia, showed marked evidence of increased bone marrow activity, i. e., a high color index, polychromatophilia, and blasts, from which one may infer that there was active blood destruction going on.

Case (a) of group "B" gave a history which would pass for pernicious anemia and showed a blood picture strikingly like that seen in this disease, i. e., a color index above 1, polychromatophilia, macrocytes, etc., except that many of the red cells showed definite achromia. It was found that he had internal hemorrhoids which had bled at times since the onset of the present illness, but never very much, nor was the increase in anemia associated with any increased bleeding. The



normal urobilin output, however, was strongly in favor of this being a secondary anemia. Treatment was directed toward eliminating this possible etiologic factor with the result that within three weeks after operation on his hemorrhoids, the anemia had almost disappeared.

Case (b) showed a somewhat changing blood picture. Two months previous to admission a relative and absolute lymphocytosis had been found. During his first stay in the hospital the blood was indistinguishable from that seen in pernicious anemia and he was discharged with this diagnosis. *The normal urobilin output found in this case was against pernicious anemia.* After a few weeks he entered the hospital again in a poorer condition and with marked dyspnea. The only changes in the blood were a marked increase in the number of normoblasts—as high as 70 per cent. per 100 white cells—and the presence of an occasional myelocyte. At this time an enlarged and nodular prostate was felt and X rays of the bones and lungs gave a picture strongly suggesting diffuse metastatic malignant disease. Our final diagnosis of carcinoma of the prostate with extensive bone marrow involvement would explain the very unusual blood picture as well as the anemia of a nonhemolytic type. For, according to Dr. J. H. Wright, the replacement of his red bone marrow by metastatic tumor tissue produced not only the anemia, but also caused hematopoiesis in the liver and spleen and consequently a fetal type of blood, i. e., large numbers of normoblasts in the circulation.

The remaining four cases in group "B" all showed a diminution in blood production—a low color index, achromia and no blasts.

*Grave Anemia.*—Questionably pernicious or early leukemia. This was another case of atypical anemia diagnosed as pernicious during life. The blood picture was in every way characteristic of this disease; however, several weeks before death the spleen began to enlarge and within a short time had filled the entire left side. At autopsy the glands were found to be filled with myelocytes and the spleen and bone marrow showed large areas of myelocyte formation.

*Leukemia.*—All three cases were treated with radium at the Combs P. Huntington Memorial Hospital and in two the urobilin was determined before and during the course of the treatment. Of particular interest is the fact that during the three weeks of radium application, the white count in one dropped from 640,000 to 94,000 and in the other from 700,000 to 340,000, yet the urobilin remained the same, instead of increasing as might be expected, and the red counts showed an upward tendency. The absence of any change in urobilin output shows conclusively that radium does not destroy red cells, but rather

stimulates their formation. It would be difficult to demonstrate in any other way that the increased red cell production was not accompanied by an increased destruction which might have acted to stimulate the bone marrow.<sup>5</sup>

*Biliary Cirrhosis.*—The low figures in these two cases are of interest in view of the increased urobilin output which Eppinger found in hypertrophic cirrhosis. All clinical evidence supported the normal estimation to prove that the jaundice present was of hepatic and not of hemolytic origin.

Case "B" called "splenic" in type, for want of a better name, as there was marked enlargement of the spleen without apparent etiology or accompanying anemia, gave a history which might well have passed for one of congenital hemolytic jaundice. Yet the slight enlargement of the liver, the presence of bile in the urine, the absence of increased fragility, and the small percentage of reticulated cells, together with the normal urobilin output, definitely excluded abnormal blood destruction as the cause of his jaundice.

*Banti's Disease.*—There is no uniformity in the degree of blood destruction occurring in Banti's disease. Certain cases, or possibly stages, of the process show an increase, others do not. It is impossible to say as yet what these variations signify, since there are such a small number of reported cases of Banti's disease in which urobilin estimations have been made. Eppinger, however, who has studied the disease from this point of view, has the feeling that those cases which gave high urobilin estimations showed the most favorable results after splenectomy.

*Chronic Passive Congestion.*—There was no reason to suppose that an increased urobilin output would be found in this condition. I made the estimations on these patients because Eppinger and Charnas have reported high figures in chronic passive congestion. A possible explanation of this discrepancy in results may be the fact that their two cases were evidently *in extremis*, while those in the above table had well marked decompensation but were not dangerously ill.

*Pneumonia.*—If the jaundice present in these two cases were of hemolytic origin, one would expect the urobilin to be somewhere in the neighborhood of the estimation shown by congenital hemolytic jaundice. That it was within normal limits seems strong evidence in favor of a hepatogenous origin.

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5. The effect of radium on the blood in these cases, and also the findings in the case of "grave" anemia are cited by the kind permission of Dr. Thomas Ordway.

*Post-Transfusion Toxemia—Jaundice.*—This was a patient with hemophilia who had a severe reaction after transfusion, followed in thirty-six hours by a moderate jaundice and almost complete suppression of urine. At first sight it seemed that a marked hemolysis had occurred. However, there was no increase in the anemia present before transfusion, the urine obtained on the second day contained bile and urobilin but no hemoglobin, and jaundice persisted for ten days, when death supervened. The low urobilin output added valuable information, and, together with the above facts, made it apparent that the condition was a toxemia affecting the liver and kidneys especially and that the jaundice was due to marked hepatic insufficiency. Autopsy showed central degeneration of the liver lobules and acute interstitial nephritis.

*Paroxysmal Hemoglobinuria.*—Paroxysms were produced in this patient several times, and in spite of the very evident free hemoglobin present in the blood serum afterwards, the urobilin output was not increased. This rather puzzling condition was explained by determining the rate of hemoglobin excretion by the kidneys, which was found to be exceedingly rapid—over 90 per cent. of the hemoglobin set free was eliminated in the first two hours."

*Tarry Stools.*—These stools were selected in order to determine whether the blood pigments in cases of increased hemolysis might not pass into the intestine as such, and there be broken down directly into urobilin, without having to go through the intermediary stage of bile formation. If this were the case, blood in the stools would be a serious factor of error in urobilin determinations. The low readings here rule out this possibility.

#### SUMMARY AND CONCLUSIONS

1. An increased quantity of urobilin in the stool was found constantly in 11 cases of pernicious anemia (except during remission); also in congenital hemolytic jaundice, malaria, and in one case of secondary anemia with a regenerative type of blood. All these cases showed clinical evidence of increased blood destruction.
2. Cases of leukemia, secondary anemia, chronic passive congestion, pneumonia with jaundice, and diseases of the liver, all showed a urobilin output within the limits found in normal individuals.
3. Those patients in whom the evidence of blood destruction was most marked, gave the highest urobilin estimations.
6. A more complete report of this case will be made later

4. There was no case with a normal urobilin output which showed any evidence of abnormal hemolytic activity.

5. In view of the consistency of the above results, it seems fair to conclude, first, that the quantity of urobilin in the stool may be taken as an approximate measure of the degree of hemolysis occurring in the body, and second, that such estimation is of very definite clinical value in the diagnosis of conditions questionably hemolytic in character, particularly in anemias of uncertain type.

## THE EFFECT OF REPEATED INJECTIONS OF FOREIGN PROTEIN ON THE HEART MUSCLE \*

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During some investigations previously reported,<sup>1</sup> dealing with the effect of repeated injections of foreign protein on the kidneys and liver of experimental animals, it was noted that changes frequently occurred in the heart muscle; and at that time mention was made of this fact. Since then the study of chronic protein intoxication and the effect of repeated anaphylactic shocks in animals, has been continued, and as one part of the investigation especial attention has been paid to the change in the myocardium.

That certain disturbances in the function of heart muscle may accompany acute anaphylactic shock is already well established. Auer and Robinson<sup>2</sup> have observed in both dogs and rabbits, marked alterations in rhythm, delay in the conduction of impulse from auricle to ventricle and partial or complete block during the acute phase of anaphylactic shock. Auer<sup>3</sup> also describes a waxy appearance of the myocardium and of the voluntary muscles of the leg in rabbits dying under the same conditions.

Worzekowsky and Kundratitz<sup>4</sup> have observed swelling, granulation and loss of cross striation in the muscle fibers of the heart following acute anaphylactic shock in guinea-pigs, while much the same changes are described by Beneke and Steinschneider.<sup>5</sup>

The details of the technic for these experiments are fully described in the previous article. Suffice it to say that rabbits, dogs, cats and guinea-pigs were sensitized to egg-white alone, horse serum alone, or to both proteins, and after an interval of three weeks inoculated with intoxicating doses of these foreign proteins. An attempt was always made to administer a dose sufficiently large to produce symptoms, but not large enough to kill.

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\* Submitted for publication March 6, 1915.

<sup>2</sup> From the Medical Clinic of Columbia University, Presbyterian Hospital, New York.

1. Longcope, W. T.: *Jour. Exper. Med.*, 1913, xviii, 678.

2. Auer and Robinson: *Jour. Exper. Med.*, 1913, xviii, 42.

3. Auer: *Ztschr. f. Physiol.*, 1913, xxviii, 383.

4. Worzekowsky and Kundratitz: *Arch. f. exper. Path. u. Pharmakol.*, 1913, lxxiii, 33.

5. Beneke and Steinschneider: *Centbl. f. allg. Path.*, 1912, xxiii, 592; *Ztschr. f. allg. Path.*, 1914, xxiv, 415.

The sensitizing doses were given at times intravenously (except in guinea-pigs), at times intraperitoneally and occasionally subcutaneously. The intoxicating doses were administered either intravenously or intraperitoneally. The number of intoxicating doses varied from three to twenty. In the majority of cases the animals received six to twelve intoxicating doses at intervals of one to two weeks.



Fig. 1.—Rabbit 24. Effect of repeated injections of egg white on heart of sensitized rabbit. Extensive focal infiltration of myocardium by small round cells.

As controls many hearts from rabbits and guinea-pigs that were supposedly normal have been examined, and a moderate number of hearts from dogs and cats. As a part of the study, rabbits have also been inoculated with a single dose of horse serum or egg white and their organs examined after varying intervals of time.



The material comprises the organs from 54 rabbits, 33 of which were sensitized and later received repeated intoxicating injections of foreign protein, 22 of which received but a single large dose of foreign protein; and 11 guinea-pigs, 13 dogs and 10 cats, all subjected to repeated anaphylactic shocks.

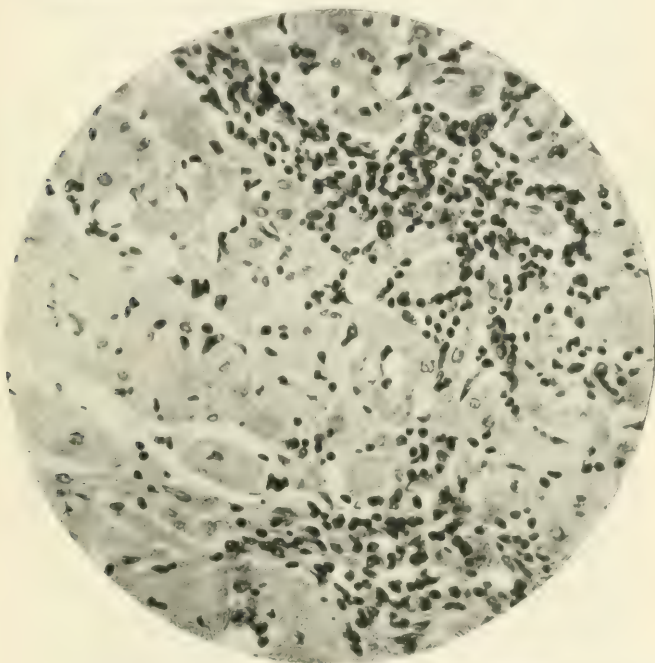


Fig. 2.—Rabbit E. I. Effect of repeated injections of egg white on myocardium of sensitized rabbit. Small focus of round cell infiltration. (High power.)

Since the changes in the myocardium are confined almost exclusively to the rabbit, these alone will be described in detail.

Of 11 guinea-pigs, 3 showed the myocardial changes to be described; of the 13 dogs one, and of the 10 cats one, whereas of the 33 rabbits subjected to repeated anaphylactic shock, 27, or 81.8 per cent., showed more or less extensive involvement of the myocardium.

Macroscopically the hearts presented little that was abnormal. In a few instances they seemed large and were dilated, but since no

accurate weights or measurements were taken, little importance can be attached to this. Frequently the heart muscle was pale or showed a slight grayish streaking, and in a few instances it was distinctly firm. Microscopically the alterations were very definite and often widespread. They were seen both in the right and left ventricle and in the auricle. Sometimes they appeared more intense in one situation than another and were particularly common and numerous in the right ventricle.

What appeared to be the earliest and certainly the smallest lesions consisted of foci in which the muscle fibers looked swollen but showed no other definite changes. Surrounding these fibers and infiltrating irregularly the reticular spaces between them, were considerable numbers of small round cells. In the larger and further advanced lesions the muscle fibers presented more definite changes indicative of degeneration. There was swelling, loss of striation, occasionally vacuolization or irregular staining of the sarcoplasm. The nuclei were swollen and took the hematoxylin stain poorly. In marked contrast, however, to these comparatively slight alterations in the muscle fibers, was the extensive infiltration of small round cells which was always present. About the margins of the degenerative muscle fibers they were densely packed and infiltrated between the muscle cells in great numbers. So large and dense were many of these foci that they could be seen by the naked eye in sections stained by hematoxylin and eosin, when they stood out as sharply marked blue points. In the foci where the infiltration was most pronounced the degeneration of the muscle cells was most marked. Here and there the fibers in cross section showed as an indefinite, shrunken mass of protoplasm, staining rather deeply in eosin. Rarely the fibers had disappeared entirely.

In the most advanced stage of this subacute process, the focus appeared as a mass of small round cells, amongst which were scattered the remains of the muscle fibers.

What was taken to be the final stage of this focal chronic inflammatory process was a group of swollen, irregular vacuolated muscle fibers embedded in a mesh of connective tissue, infiltrated here and there with small round cells or epithelioid cells.

The lesions which have just been described were seen in all parts of the heart muscle. They occurred beneath the endocardium, especially of the right ventricle, as well as in the depths of the muscle. They were rarely, if ever, situated about blood vessels, and the smaller arteries as well as the capillaries within and surrounding the foci were normal. Thrombi were never observed.

As a rule the heart muscle between these foci and a short distance from them was normal, though in the right ventricle especially there was occasionally to be seen some edema and slight diffuse infiltration

of small round cells. In the latter stages of the process, too, when the cellular infiltration was largely replaced by connective tissue, the margin of the focus was not well defined and when many such areas occurred the appearance, especially in the right ventricle, was that of a more or less diffuse interstitial myocarditis.

One may characterize these changes, then, as a slowly progressing degeneration of muscle fibers in isolated foci, accompanied very early by an intense round cell infiltration, and finally healing as connective tissue scars. They are not associated with discoverable changes in the blood vessels or capillaries. They vary in number from one to seven or eight in a single section and in size from the involvement of a few muscle fibers to foci measuring 0.5 to 1 mm. in diameter.

Though a great number of hearts from normal rabbits have been carefully studied, no such changes have ever been observed. Indeed, in one lot of thirty-six rabbits which were used for some of these experiments, all arriving at the same time from a single dealer, twelve were killed as controls and the hearts of all were normal. It seems justifiable, therefore, to conclude that the lesions which have been described are in some way dependent on the introduction of foreign protein into the circulation of these animals. The total absence of thrombi or vascular abnormalities excludes the possibility of capillary thrombosis as a cause.

To compare the results obtained in sensitized rabbits subjected to repeated anaphylactic shocks, the hearts from twenty-two rabbits which had received but a single dose of horse serum or egg white, or at most three injections repeated at twenty-four to forty-eight hour intervals, were examined at varying intervals after the injection had been made. This experiment revealed the fact that occasionally these animals showed the same changes as those repeatedly inoculated. Thus in this series of twenty-two animals the hearts of eight rabbits, or 25 per cent., showed similar but much less marked changes. The foci of degeneration and infiltration were fewer, so that often only one or two could be found after searching through several sections, and they were much smaller. This observation is sufficient to show, however, that subacute inflammatory foci do occur in the heart muscle of rabbits after a single injection of egg white or horse serum.

This brings up the question as to whether the alterations described are dependent on a primary toxic action of foreign proteins when introduced parenterally on the cells of animals, or whether the lesions are dependent on an injury which occurs only during the period of anaphylactic shock. In a later publication this question will be fully dealt with, but suffice it to say at present that the occasional appearance of the lesions indicated in animals receiving but a single injection

of a large amount of foreign protein, does not justify the assumption that the entire process is caused by the primary toxic action of the foreign protein. In man, at least, the single injection of a foreign protein is followed, in many instances, after an interval of seven to ten days, by "serum sickness," a condition often of severe intoxication which von Pirquet and Schick have shown to be an anaphylactic phenomenon. Though the symptom complex known as serum disease is not observed in animals, it is still possible that an analogous condition accompanied by an injury to certain cells of the body may follow the single injection of foreign protein in any animal.

It is well known that the injection of certain toxic substances will produce extensive myocarditis in rabbits. Epinephrin and spartein have been shown by Loeb to bring about alteration in the heart muscle of rabbits. These changes, however, are entirely different from the ones obtained in my experiments.

Perhaps more nearly allied, but still not identical, are the focalized degenerative and productive lesions obtained by several observers in the hearts of rabbits after the intravenous injection of certain types of streptococci. Thalheimer and Rothschild<sup>6</sup> have recently reviewed the literature on this subject and have described quite accurately such myocardial changes. The lesions thus produced differ principally from those that I have obtained in the degree of necrosis of the muscle fiber and polymorphonuclear leukocytic infiltration, which in my sections was entirely absent.

#### CONCLUSIONS

Repeated intoxicating injections of foreign proteins in rabbits previously sensitized to these substances causes extensive focal degeneration of the cells of the heart muscle as well as of the kidney and liver. In the heart muscle these areas are characterized early by a dense infiltration of small round cells. Later the foci of subacute inflammation give place to scar formation, so that in some instances the appearance of interstitial myocarditis is produced.

Though these changes in the myocardium are only widespread and only occur regularly after repeated injections of foreign protein in sensitized animals, they may occasionally be found in rabbits that have received a single injection of foreign protein.

This does not necessarily mean that the protein is primarily toxic for the cells of the animal.

The lesions are quite different from those produced by injections of epinephrin and do not correspond exactly with the descriptions of those obtained from injections of streptococci.

680 Madison Avenue.

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6. Rothschild and Thalheimer: *Jour. Exper. Med.*, 1914, xix, 429.

# INDEX TO VOLUME XV

	PAGE
Abderhadden reaction, observations on the use of the, with normal and pathological human serums; Ellison L. Ross and H. Douglas Singer..	724
Aconite, tincture of, an investigation of the potency of; G. Canby Robinson	645
• Addis, T.: A working hypothesis of hemoglobin pigment metabolism.....	413
Anders, James M.: Book Review.—A text-book of medical diagnosis.....	178
Anemia, primary pernicious, the factors of coagulation in; Cecil K. Drinker and Samuel H. Hurwitz .....	733
Asthma and emphysema, the ventilatory function of the lung in; C. F. Hoover and Lester Taylor .....	1
• Atchley, Dana W.: Nuclear digestion and uric acid excretion in a case of total occlusion of the pancreatic duct.....	654
Atophan and novatophan, action of, in gout and iritis; C. A. Smith and P. B. Hawk.....	181
• Baetjer, W. A.: Further studies of renal function in renal, cardiorenal and cardiac diseases .....	543
Bateson, William: Book Review.—Problems of genetics.....	178
Bibb, L. B.: Skiagraphic study of thorax, thoracic wall and thoracic viscera	558
Birdsall, J. C.: Further observations on the employment of specific and non-specific antigens in the performance of the gonococcal complement-fixation test .....	265
Blastomycosis and coccidioidial granuloma, a differential study of. I. Pathology and bacteriology. II. Report of two additional cases of coccidioidial disease; Philip King Brown and W. Taylor Cummins.....	608
Blood-pressure: Its clinical applications, by George William Norris; book review .....	177
Body, human, specific gravity of the; C. D. Spivak.....	628
Book Review: A text-book of medical diagnosis; James M. Anders and L. Napoleon Boston.....	178
Book Review: Chemical pathology; H. Gideon Wells .....	643
Book Review: Blood-pressure: Its clinical applications; George William Norris .....	177
Book Review: Disease and its causes; W. T. Councilman.....	177
Book Review: L'alternance du coeur: Etude critique; par Laurent Gravier	339
Book Review: Problems of genetics; William Bateson .....	178
Book Review: The life and letters of Nathan Smith; Emily A. Smith; introduction by William H. Welch .....	340
Book Review: The mental health of the school child; J. E. Wallace Wallin .....	177
Boston, L. Napoleon: Book Review.—A text-book of medical diagnosis....	178

# INDEX TO VOLUME XI

	PAGE
Bridgman, E. W.: The value of the electrocardiogram in the diagnosis of cardiac hypertrophy .....	487
Brooks, Barney: Intestinal obstruction. An experimental study of the causes of symptoms and death.....	392
Brown, Philip King: A differential study of coccidioidal granuloma and blastomycosis. I. Pathology and bacteriology. II. Report of two additional cases of coccidioidal disease.....	608
Cabot, Hugh: The effect of anesthesia and operation on the kidney function, as shown by the phenolsulphonephthalein test.....	369
Caffein and strychnin, the use of, as cardiovascular stimulants in the acute infectious diseases; L. H. Newburgh.....	458
Calcification, metastatic; H. Gideon Wells.....	574
Calorimetry, clinical. First paper. A respiration calorimeter for the study of disease; Graham Lusk.....	793
Calorimetry, clinical. Second paper. The respiration calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital; J. A. Riche and G. F. Soderstrom.....	805
Calorimetry, clinical. Third paper. The organization of a small metabolism ward; Frank C. Gephart and Eugene F. DuBois.....	829
Calorimetry, clinical. Fourth paper. The determination of the basal metabolism of normal men and the effect of food; Frank C. Gephart and Eugene F. DuBois .....	835
Calorimetry, clinical. Fifth paper. The measurement of the surface area of man; Delafield DuBois and Eugene F. DuBois.....	868
Calorimetry, clinical. Sixth paper. Notes on the absorption of fat and protein in typhoid fever; Warren Coleman and Frank C. Gephart.....	882
Calorimetry, clinical. Seventh paper. Calorimetric observations on the metabolism of typhoid patients with and without food; Warren Coleman and Eugene F. DuBois.....	887
Calorimetry, clinical. Eighth paper. On the diabetic respiratory quotient; Graham Lusk .....	939
Cameron, A. L.: The origin of the proteins of nephritic urine.....	746
Cancer, human, a study of general and localized effects of intravenous injections of colloidal copper and casein in cases of; C. B. McClurg, W. O. Sweek, H. N. Lyon, M. S. Fleisher and Leo Loeb.....	974
Cardiac hypertrophy, the value of the electrocardiogram in the diagnosis of; E. W. Bridgman.....	487
Cecil, Russell L.: Streptococcus viridans in its relation to infections of the upper respiratory tract.....	150
Chloroform, variations in the toxicity of, for anesthesia; Worth Hale.....	945
Coccidioidal granuloma, immunity tests in; Jean V. Cooke.....	479
Coeur, l'alternance du, par Laurent Gravier: Etude critique; book review..	339
Coleman, Warren: Clinical calorimetry. Sixth paper. Notes on the absorption of fat and protein in typhoid fever.....	882
Coleman, Warren: Clinical calorimetry. Seventh paper. Calorimetric observations on the metabolism of typhoid patients with and without food....	887
Colitis, chronic ulcerative, with polyps. A consideration of the so-called colitis polyposa (Virchow); J. H. Hewitt and W. T. Howard.....	714



## INDEX TO VOLUME XI

	PAGE
Cooke, Jean V.: Immunity tests in coccidioidal granuloma.....	479
Councilman, W. T.: Book Review.—Disease and its causes.....	177
• Crohn, Burrill B.: Studies in pancreatic disease.....	581
Crohn, Burrill B.: Rat-bite fever .....	1014
Cummins, W. Taylor: A differential study of coccidioidal granuloma and blastomycosis. I. Pathology and bacteriology. II. Report of two additional cases of coccidioidal disease.....	608
• Daniels, Amy L.: The relation of uric acid to gouty attacks.....	1046
Davis, David John: The effects of sodium salicylate on various types of experimental arthritis .....	555
Diabetes insipidus, experimental, in dogs; S. A. Matthews.....	451
Diabetic respiratory quotient, on the, clinical calorimetry, eighth paper; Graham Lusk .....	939
Diagnosis, medical, a text-book of; by James M. Anders and L. Napoleon Boston; book review.....	178
Disease and its causes, by W. T. Councilman; book review.....	177
Draper, George: Effect of intravenous and intraspinal treatments on cerebrospinal syphilis .....	16
Drinker, Cecil H.: The factors of coagulation in primary pernicious anemia	733
DuBois, Delafield: Clinical calorimetry. Fifth paper. The measurement of the surface area of man.....	868
• DuBois, Eugene F.: Clinical calorimetry. Third paper. The organization of a small metabolism ward.....	829
DuBois, Eugene F.: Clinical calorimetry. Fourth paper. The determination of the basal metabolism of normal men and the effect of food.....	835
DuBois, Eugene F.: Clinical calorimetry. Fifth paper. The measurement of the surface area of man.....	868
• DuBois, Eugene F.: Clinical calorimetry. Seventh paper. Calorimetric observations on the metabolism of typhoid patients with and without food .....	887
Eckhardt, Engelhardt A.: Factors involved in some cases of pleural fluid associated with normal or increased vocal resonance.....	1040
Edema, paroxysmal, studies in; Walter W. Palmer.....	329
Emphysema and asthma, the ventilatory function of the lung in; C. H. Hoover and Lester Taylor.....	1
Falconer, E. H.: A report of the bacteriologic examination of enlarged lymphnodes removed from a patient with Hodgkin's disease.....	438
Fibrillation, coarse auricular, in man; A. W. Hewlett and F. N. Wilson..	786
• Fitz, R.: Observations on renal function in acute experimental unilateral nephritis .....	303
• Fitz, R.: Study XXIII. The relation between amylase retention and excretion and nonprotein nitrogen retention in experimental uranium nephritis	524
Fleisher, M. S.: A study of general and localized effects of intravenous injections of colloidal copper and casein in cases of human cancer.....	974

# INDEX TO VOLUME XV

	PAGE
Foster, N. B.: Mercury nephritis .....	754
Foster, Nellis B.: Uremia III. The nonprotein nitrogen of blood.....	356
Frothingham, Channing: A study of different nitrogenous diets in chronic nephritis .....	204
Gammon, Julian E.: The dead space in moderate and large respiratory ventilation .....	501
Garrison, P. E.: Statistics of pellagra in Spartanburg County, S. C., including geographical distribution of the disease and its relation to race, age, sex and occupation.....	98
Genetics, problems of; by William Bateson; book review.....	178
Gephart, Frank C.: Clinical calorimetry. Third paper. The organization of a small metabolism ward.....	829
Gephart, Frank C.: Clinical calorimetry. Fourth paper. The determination of the basal metabolism of normal men and the effect of food...	835
Gephart, Frank C.: Clinical calorimetry. Sixth paper. Notes on the absorption of fat and protein in typhoid fever.....	882
Gilliland, C. E.: Skiagraphic study of thorax, thoracic wall and thoracic viscera .....	558
Glomset, Daniel: Malignant sympathetic tumor of the right suprarenal....	341
Gonococcic complement-fixation test, further observations on the employment of specific and nonspecific antigens in the performance of the; B. A. Thomas, R. H. Ivy and J. C. Birdsall.....	265
Granuloma, coccidioidal and blastomycosis, a differential study of. I. Pathology and bacteriology. II. Report of two additional cases of coccidioidal disease; Philip King Brown and W. Taylor Cummins....	608
Gravier, Laurent: Book Review.—L'alternance du coeur: Etude critique..	339
Hale, Worth: Variations in the toxicity of chloroform for anesthesia....	945
Hawk, P. B.: The action of atophan and novatophan in gout and iritis..	181
Heart muscle, the effect of repeated injections of foreign protein on the; W. T. Longcope .....	1079
Heart, studies on the pathological physiology of the: I. The intra-auricular, intraventricular and aortic pressure curves in auricular fibrillations; Carl J. Wiggers.....	77
Hemmeter, John C.: The radio-activity of the mineral waters of hot springs, warm springs, and healing springs in Hot Springs, Va.....	188
Hemoglobin pigment metabolism, a working hypothesis of; T. Addis.....	413
Hewitt, J. H.: Chronic ulcerative colitis with polyps. A consideration of the so-called colitis polyposa (Virchow).....	714
Hewlett, A. W.: Coarse auricular fibrillation in man.....	786
Hillman, Oliver S.: Further observations on the blood-count in pellagra..	147
Hodgkin's disease, a report of the bacteriologic examination of enlarged lymphnodes removed from a patient with; Lawrence J. Rhea and E. H. Falconer .....	438
Hoover, C. F.: The ventilatory function of the lung in emphysema and asthma .....	1
Hoover, C. F.: The dead space in moderate and large respiratory ventilation .....	501

# INDEX TO VOLUME XV

	PAGE
Hopkins, Arthur H.: Studies in renal function with special reference to non-protein nitrogen and sugar concentration in the blood, phenol-sulphonaphthalein elimination and blood pressure.....	964
Howard, W. T.: Chronic ulcerative colitis with polyps. A consideration of the so-called colitis polyposa (Virchow).....	714
Hurwitz, Samuel H.: The factors of coagulation in primary pernicious anemia .....	733
Hydronephrosis, experimental, functional changes in; N. M. Keith and R. R. Snowden.....	239
Intestinal obstruction. An experimental study of the causes of symptoms and death; Fred T. Murphy and Barney Brooks.....	392
Iodin, the distribution of, in the cell following administration of organic iodine preparations; Franklin C. McLean.....	92
Iodin, the therapeutic action of; James W. Jobling and William Petersen.	286
Ivy, R. H.: Further observations on the employment of specific and non-specific antigens in the performance of the gonococcic complement-fixation test.....	265
Jaundice, congenital hemolytic, metabolism study of a case of, with splenomegaly; James P. McKelvy and Jacob Rosenbloom.....	227
Jobling, James W.: The therapeutic action of iodine.....	286
Jonas, Leon: Studies in renal function with special reference to non-protein nitrogen and sugar concentration in the blood, phenolsulphonaphthalein elimination and blood pressure.....	964
Keith, N. M.: Functional changes in experimental hydronephrosis .....	239
Kidney function, the effect of anesthesia and operation on the, as shown by the phenolsulphonaphthalein test; Richard H. Miller in collaboration with Hugh Cabot.....	369
Kirk, Edwin Garvey: The relation of pancreatic organotherapy to ketogenesis .....	39
Levine, Samuel A.: The ocular reflex. An electrocardiographic study with special reference to the differences between right and left vagal and ocular pressures in tabetics and nontabetics .....	758
Locke, Edwin A.: Secondary hypertrophic osteo-arthritis and its relation to simple club-fingers .....	659
Loeb, Leo: A study of general and localized effects of intravenous injections of colloidal copper and casein in cases of human cancer .....	974
Loewenhardt, A. S.: Certain aspects of biological oxidation .....	165
Longcope, W. T.: The effect of repeated injections of foreign protein on the heart muscle .....	1079
Lusk, Graham: Clinical calorimetry. First paper. A respiration calorimeter for the study of disease .....	793
Lusk, Graham: Clinical calorimetry. Eighth paper. On the diabetic respiratory quotient .....	939
Lyon, H. N.: A study of general and localized effects of intravenous injections of colloidal copper and casein in cases of human cancer .....	974

# INDEX TO VOLUME XI

	PAGE
MacNeal, W. J.: Statistics of pellagra in Spartanburg County, S. C., including geographic distribution of the disease and its relation to race, age, sex and occupation.....	98
Magnesium sulphate, the relation of the purgative action of, to peristalsis and general law of crossed innervation; S. J. Meltzer.....	955
Marshall, E. K.: Further studies of renal function in renal, cardiorenal and cardiac diseases.....	543
Matthews, S. A.: Experimental diabetes insipidus in dogs.....	451
McClurg, C. B.: A study of general and localized effects of intravenous injections of colloidal copper and casein in cases of human cancer....	974
McCrudden, Francis H.: The relation of uric acid to gouty attacks.....	1046
McKelvy, James P.: Metabolism study of a case of congenital hemolytic jaundice with splenomegaly.....	227
McLean, Franklin C.: The distribution of iodine in the cell following administration of organic iodine preparations.....	92
Meltzer, S. J.: The relation of the purgative action of magnesium sulphate to peristalsis and the general law of crossed innervation.....	955
Metabolism, basal, determination of the, of normal men and the effect of food. Clinical calorimetry. Fourth paper; Frank C. Gephart and Eugene F. DuBois.....	835
Metabolism ward, small, organization of a. Clinical calorimetry. Third paper; Frank C. Gephart and Eugene F. DuBois.....	829
Miller, Richard H.: The effect of anesthesia and operation on the kidney function, as shown by the phenolsulphonephthalein test.....	369
Montgomery, Charles M.: Factors involved in some cases of pleural fluid associated with normal or increased vocal resonance.....	1040
Morris, Roger S.: The occurrence of nuclear particles in the erythrocytes following splenectomy .....	514
Murphy, Fred T.: Intestinal obstruction. An experimental study of the causes of symptoms and death.....	392
Myocardium, how shall we tell whether or not the, is competent?; John M. Swan .....	269
Neoplasms, malignant, the occurrence of, in the young as shown by an analysis of 2,000 cases of malignant neoplasms examined in the pathological laboratory of the University of Michigan; Aldred Scott Warthin.....	444
Nephritic urine, the origin of the proteins of; A. L. Cameron and H. Gideon Wells.....	746
Nephritis, acute experimental unilateral, observations on renal function in; W. C. Quinby and R. Fitz .....	303
Nephritis, chronic, a study of different nitrogenous diets in; Channing Frothingham, Jr., and Wilson G. Smillie.....	204
Nephritis, experimental uranium. Study XXIII. The relation between amylase retention and excretion and nonprotein nitrogen retention in; R. Fitz .....	524
Nephritis, mercury; N. B. Foster.....	754
Neuhof, Selian: A case of independent ventricular activity occurring during acute articular rheumatism .....	169

# INDEX TO VOLUME XV

	PAGE
Newburgh, L. H.: The use of strychnin and caffen as cardiovascular stimulants in the acute infectious diseases.....	458
Norris, George William: Book Review.—Blood-pressure: Its clinical applications .....	177
Novatophan and atophan, action of, in gout and iritis; C. A. Smith and P. B. Hawk.....	181
Nystagmus, labyrinthine, the mechanism of, and its modifications by lesions in the cerebellum and cerebrum; J. Gordon Wilson and F. H. Pike....	31
Ocular reflex. An electrocardiographic study with special reference to the differences between right and left vagal and ocular pressures in tabetics and nontabetics; Samuel A. Levine.....	758
O'Hare, James P.: Study XXIV: The effect of theobromin sodium salicylate in acute chromatic nephritis .....	1053
Osteo-arthropathy, secondary hypertrophic, and its relation to simple club-fingers; Edwin A. Locke .....	659
Oxidation, biological, certain aspects of; A. S. Loevenhart.....	1059
Palmer, Walter W.: Studies in paroxysmal edema.....	329
Pancreatic disease, studies in; Burrill B. Crohn.....	581
Pancreatic duct, nuclear digestion and uric acid excretion in a case of total occlusion of the; Dana W. Atchley.....	654
Pancreatic organotherapy, the relation of, to ketogenesis; Edwin Garvey Kirk .....	39
Pathology, chemical, by H. Gideon Wells; book review.....	643
Pellagra, further observations on the blood count in; Oliver S. Hillman and Paul A. Schule.....	147
Pellagra, mental and nervous disorders associated with; H. Douglas Singer	121
Pellagra, statistics of, in Spartanburg County, S. C., including geographic distribution of the disease and its relation to race, age, sex and occupation; J. F. Siler, P. E. Garrison and W. J. MacNeal.....	98
Petersen, William: The therapeutic action of iodine.....	286
Pike, F. H.: The mechanism of labyrinthine nystagmus and its modifications by lesions in the cerebellum and cerebrum.....	31
Quinby, W. C.: Observations on renal function in acute experimental unilateral nephritis.....	303
Radio-activity of the mineral waters of hot springs, warm springs and healing springs in Hot Springs, Va.; John C. Hemmelter and Ernest Zueblin .....	188
Rat-bite fever; Burrill B. Crohn.....	1014
Renal function, further studies of, in renal, cardiorenal and cardiac diseases; L. G. Rowntree, E. K. Marshall and W. A. Baetjer .....	543
Renal function, studies in, with special reference to non-protein nitrogen and sugar concentration in the blood, phenolsulphonethalein elimination and blood pressure; Arthur H. Hopkins and Leon Jonas .....	964
Respiration calorimeter for the study of disease. Clinical calorimetry. First paper; Graham Lusk .....	793

# INDEX TO VOLUME XI

	PAGE
Respiration calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital. Clinical calorimetry. Second paper; J. A. Riche and G. F. Soderstrom.....	805
Respiratory quotient, diabetic. Clinical calorimetry. Eighth paper; Graham Lusk.....	939
Respiratory ventilation, moderate and large, the dead space in; C. F. Hoover and Julian E. Gammon.....	501
Rhea, Lawrence J.: A report of the bacteriologic examination of enlarged lymph nodes removed from a patient with Hodgkin's disease.....	438
Rheumatism, acute articular, a case of independent ventricular activity occurring during; Selian Neuhof.....	169
Riche, J. A.: Clinical calorimetry. Second paper. The respiration calor- imeter of the Russell Sage Institute of Pathology in Bellevue Hospital	805
Robertson, Oswald H.: Urobilin in the stool—an index to blood destruc- tion .....	1072
Robinson, G. Canby.: An investigation of the potency of tincture of aconite	645
Rosenbloom, Jacob.: Metabolism study of a case of congenital hemolytic jaundice with splenomegaly.....	227
Ross, Ellison L.: Observations on the use of the Abderhalden reaction with normal and pathologic human serums.....	724
Rowntree, L. G.: Further studies of renal function in renal, cardiorenal and cardiac diseases.....	543
Sarcoma, age incidence in; Carl Vernon Weller.....	518
School child, the mental health of the, by J. E. Wallace Wallin; book review	177
Schule, Paul A.: Further observations on the blood-count in pellagra.....	147
Siler, J. F.: Statistics of pellagra in Spartanburg County, S. C., including geographic distribution of the disease and its relation to race, age, sex and occupation.....	98
Singer, H. Douglas: Mental and nervous disorders associated with pellagra.	121
Singer, H. Douglas: Observations on the use of the Abderhalden reaction with normal and pathologic human serums.....	724
Smillie, Wilson G.: A study of different nitrogenous diets in chronic nephritis .....	204
Smith, C. A.: Action of atophan and novatophan in gout and iritis.....	181
Smith, Emily A.: Book Review.—The life and letters of Nathan Smith, with introduction by William H. Welch.....	340
Smith, Nathan, the life and letters of, book review by Emily A. Smith, with introduction by William H. Welch.....	340
Snowden, R. R.: Functional changes in experimental hydronephrosis.....	239
Soderstrom, G. F.: Clinical calorimetry. Second paper. The respiration calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital .....	805
Sodium salicylate, the effects of, on various types of experimental arthritis; David John Davis.....	555
Spivak, C. D.: The specific gravity of the human body.....	628
Splenectomy, the occurrence of nuclear particles in the erythrocytes fol- lowing; Roger S. Morris.....	514



# INDEX TO VOLUME XI

	PAGE
Streptococcus viridans in its relation to infections of the upper respiratory tract; Russell L. Cecil.....	150
Strychnin and caffein, the use of, as cardiovascular stimulants in the acute infectious diseases; L. H. Newburgh.....	458
Study XXIV: The effect of theobromin sodium salicylate in acute chromate nephritis; James P. O'Hare .....	1053
Suprarenal, right, malignant sympathicus tumor of the; Daniel J. Glomset.	341
Surface area of man, measurement of the. Clinical calorimetry. Fifth paper; Delafield DuBois and Eugene F. DuBois.....	868
Swan, John M.: How shall we tell whether or not the myocardium is competent? .....	269
Sweek, W. O.: A study of general and localized effects of intravenous injections of colloidal copper and casein in cases of human cancer....	974
Syphilis, cerebrospinal, effect of intravenous and intraspinal treatments on; George Draper .....	16
Taylor, Lester: The ventilatory function of the lung in emphysema and asthma .....	1
Thomas, B. A.: Further observations on the employment of specific and nonspecific antigens in the performance of the gonococcic complement-fixation test .....	265
Thorax, thoracic wall and thoracic viscera, skiagraphic study of; L. B. Bibb and C. E. Gilliland.....	558
Typhoid fever, notes on the absorption of fat and protein in. Clinical calorimetry. Sixth paper. Warren Coleman and Frank C. Gephart....	882
Typhoid patients, calorimetric observations on the metabolism of, with and without food. Clinical calorimetry. Seventh paper; Warren Coleman and Eugene F. DuBois.....	887
Uremia III. The nonprotein nitrogen of blood; Nellis B. Foster.....	356
Uric acid, the relation of, to gouty attacks; Amy L. Daniels and Francis H. McCrudden .....	1046
Urine, nephritic, the origin of the proteins of; A. L. Cameron and H. Gideon Wells .....	746
Urobilin in the stool — an index to blood destruction; Oswald H. Robertson .....	1072
Vocal resonance, normal or increased, factors involved in some cases of pleural fluid associated with; Charles M. Montgomery and Englehardt A. Eckhardt .....	1040
Wallin, J. E. Wallace: Book Review.—Blood-pressure: Its clinical applications .....	177
Warthin, Aldred Scott: The occurrence of malignant neoplasms in the young as shown by an analysis of 2,000 cases of malignant neoplasms examined in the pathologic laboratory of the University of Michigan..	444
Welch, William: Introduction to the life and letters of Nathan Smith....	340
Weller, Carl Vernon: Age incidence in sarcoma .....	518
Wells, H. Gideon: Book Review.—Chemical pathology .....	643
Wells, H. Gideon: Metastatic calcification .....	574

# INDEX TO VOLUME XI

	PAGE
Wells, H. Gideon: The origin of the proteins of nephritic urine.....	746
Wiggers, Carl J.: Studies on the pathologic physiology of the heart. I. The intra-auricular, intraventricular and aortic pressure curves in auricular fibrillations .....	77
Wilson, F. N.: Coarse auricular fibrillation in man.....	786
Wilson, J. Gordon: The mechanism of labyrinthine nystagmus and its modifications by lesions in the cerebellum and cerebrum.....	31
Zueblin, Ernest: The radio-activity of the mineral waters of hot springs, warm springs and healing springs in Hot Springs, Va.....	188



1072

1072

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